CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213756Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 122851

MEETING MINUTES

AstraZeneca Pharmaceuticals LP
Attention: Jamie Gillette, MSc, RAC
Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

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

We also refer to the meeting between representatives of your firm and the FDA on June 28, 2019, to discuss a proposed NDA for the treatment of pediatric patients age 3 years and above, with neurofibromatosis type 1 symptomatic and/or progressive, inoperable plexiform neurofibroma based on the results of Study 11-C-0161, "A Phase I/II Study of the Mitogen Activated Protein Kinase (MEK)1 Inhibitor Selumetinib in Children with Neurofibromatosis Type I and Inoperable Plexiform Neurofibromas (SPRINT)."

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, please call me at 301-796-2320 or email sharon.sickafuse@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: pre-NDA

Meeting Date: June 28, 2019

Application Number: IND 122851
Product Name: Selumetinib
Indication: Treatment of pediatric patients age 3 years and above, with neurofibromatosis type 1 symptomatic and/or progressive, inoperable plexiform neurofibroma.
Sponsor Name: AstraZeneca Pharmaceuticals, LP (AZ)

Meeting Chair: Suzanne Demko
Meeting Recorder: Sharon Sickafuse

FDA ATTENDEES

Office of Hematology and Oncology Products
Division of Oncology Products 2
Denise Casey, M.D., Clinical Reviewer
Suzanne Demko, P.A.-C., Clinical Team Leader
Sharon Sickafuse, M.S., Regulatory Project Manager
Ashley Ward, M.D., Acting Associate Director

Division of Hematology Oncology Toxicology
Sachia Khasar, Ph.D., Nonclinical Reviewer
Whitney Helms, Ph.D., Nonclinical Team Leader

Office of Biostatistics
Division V
Yuan-Li Shen, Ph.D., Biostatistics Team Leader
Mengdie Yuan, Ph.D., Biostatistics Reviewer

Office of Product Quality
Office of New Drug Products
Division of New Drug Products 1
Olen Stephens, Ph.D. (via teleconference), OPQ Reviewer

SPONSOR ATTENDEES

In person:
AstraZeneca
Tracy Cunningham, M.D., Global Clinical Lead
Vincent Haddad, Biometrics Team Leader
Ali Khalil, M.D., Global Safety Physician
George Kirk, Ph.D., Global Medicines Lead
Jamie Gillette, MSc, RAC, United States Regulatory Lead
Carol McConnell, BPharm, Global Regulatory Lead
Karen So, M.D., Study Physician

National Cancer Institute, Cancer Therapy Evaluation Program
Austin Doyle, M.D., Medical Officer
Malcolm Smith, M.D., Associate Branch Chief, Pediatric Oncology

National Cancer Institute, Pediatric Oncology Branch
Andrea Gross, M.D., Assistant Research Physician
Brigitte Widemann, M.D., Principal Investigator, SPRINT, and Chief, National Cancer Institute Pediatric Oncology Branch
Pam Wolters, Ph.D., Staff Scientist, SPRINT

Merck & Co, Inc.
Nageatte Ibrahim, M.D., Clinical Research
Catherine Kohler, Pharm D., Director, Global Regulatory Affairs

Via teleconference:
AstraZeneca:
Kathryn Groeninger, RAC, Associate Regulatory Project Director
Dakshayini Kulkarni, Ph.D., Pharmacovigilance Scientist
Debbie Mackenzie, Executive Regulatory Affairs Director, Oncology
Diane S. Alleva, Ph.D., Director, Global Regulatory Affairs, CMC
David Carlile, Ph.D., Clinical Pharmacology Lead
Mei Dey, Ph..D, Associate Director, Oncology Biometrics - Programming
Andrew Brown, Global Imaging Lead

NIH:
Andrea Baldwin, CNP, SPRINT Project Manager
Trish Whitcomb, R.N., Clinical Program Administrator
Eva Dombi, M.D., Staff Scientist
Andrea Gillespie, R.N., Research Nurse
Jennifer Desanto, R.N., Research Nurse
Janet Therrien, SPRINT Data Manager
Oxana Kapustina, SPRINT Data Manager

BACKGROUND

On March 18, 2019, AZ submitted a meeting request (SDN 39) to discuss a proposed NDA for the treatment of pediatric patients age 3 years and above, with neurofibromatosis type 1 (NF1) symptomatic and/or progressive, inoperable plexiform neurofibroma (PN), based on the results of Study 11-C-0161, "A Phase I/II Study of the Mitogen Activated Protein Kinase (MEK)1 Inhibitor Selumetinib in Children with Neurofibromatosis Type I and Inoperable Plexiform Neurofibromas (SPRINT)." The SPRINT study is being conducted under an IND held by the National Cancer Institute's (NCI) Cancer Therapy Evaluation Program (CTEP). The meeting package was submitted on May 29, 2019, as SDN 42.

Regulatory History

On September 8, 2014, a Pre-IND/EOP1 meeting was held between FDA and AZ to discuss the development program for selumetinib for pediatric patients with inoperable NF1-related PN and to share the preliminary clinical information from the ongoing NCI-sponsored SPRINT trial.

On July 17, 2017, AZ submitted IND122851 with an open-label, single-arm, multicenter intermediate access study for patients between 2 and 18 years of age with NF1 who have inoperable, progressive, symptomatic PN and no available alternative treatments.

On November 2, 2017, FDA and AZ met to discuss the planned analyses for overall response rate (ORR), duration of response (DOR), safety, patient reported outcomes (PROs), and functional outcomes from the SPRINT trial. FDA agreed that if the data from the NCI natural history study provided sufficient evidence that spontaneous tumor regression or spontaneous reductions in PN-related morbidities do not occur as part of the natural history of disease, the observed effects (on NF1-related PN shrinkage) in the SPRINT trial could be reliably attributed to the selumetinib treatment effect. FDA agreed that the planned descriptive analyses of the changes in the functional evaluations and PROs could be used as supportive data in characterizing the clinical benefit of selumetinib. FDA recommended an additional response analysis after all patients have prolonged follow-up to better characterize the ORR and durability of response. FDA stated that the general expectation for imaging endpoints used in a single-arm trial intended to support approval is blinded independent confirmation of the ORR and DOR results.

On February 14, 2018, FDA granted Orphan Drug designation to selumetinib for the treatment of neurofibromatosis Type 1.

On July 18, 2018, FDA and AZ met to discuss potential trial conduct and data quality issues based on AZ's conduct of quality assurance audits of the SPRINT trial sites and the proposed risk mitigation plans to ensure reliability of the data. FDA generally agreed that AZ's plans to address potential trial conduct issues appeared reasonable; however, FDA stated that whether the mitigation procedures can allow for full confidence in the

reliability of the results to support marketing approval will be determined during review of the application.

On November 13, 2018, FDA issued a WRO letter regarding the structure, content, and format of the proposed NDA. The following key points were included in the letter:

FDA agreed:

- With the plan to reference tumor volume data from NCI's NF1 Natural History study and the placebo arm from Phase A of the NCI Pediatric Oncology Branch (POB)-coordinated study (01-C-0222) as external controls for tumor growth and for the efficacy endpoints of progression free survival (PFS) and time to progression (TTP), respectively. FDA noted, however, that these analyses are considered exploratory.

- With the determination of ORR via a blinded independent review of images (per (b) (4)). FDA stated that, in general, the results of the independent review of ORR and DOR are used for the primary regulatory analysis in the context of a single-arm trial.

- With the proposal to not pool the efficacy data from SPRINT Phase 1 and SPRINT Phase II Stratum 2 and that these results will be submitted and presented in a side by side summary in the Summary of Clinical Efficacy. FDA agreed that clinical study reports (CSRs) and efficacy datasets will also be submitted from both portions of the trial.

- With the plan to reference tumor volume data from NCI's NF1 Natural History study and the placebo arm from Phase A of the NCI Pediatric Oncology Branch (POB)-coordinated study (01-C-0222) as external controls for tumor growth and for the supportive efficacy endpoints of progression free survival (PFS) and time to progression (TTP). FDA noted, however, that these analyses are considered exploratory.

- With the proposal for the analyses of functional evaluations and patient-reported outcomes from SPRINT Phase II Stratum 1 based on the descriptive statistics and mixed model repeated measures (MMRM).

- With the proposal to submit individual patient reviews (IPRs) as supportive efficacy data. FDA advised AZ to include a discussion of how the change in the target function or symptom correlates with the radiographic response and the timing of response in the summary section of the IPR. FDA recommended that AZ include relevant photos (e.g., baseline and best response) and timepoints during treatment when the photos were collected in the IPR.

- With the plan to provide the pooled data from patients participating in both phases of the SPRINT trial with subgroup analyses of patients treated at the intended dose

and patients treated with any dose of selumetinib. Subgroup safety analyses based on dose level in pediatric populations and in adult populations receiving single agent selumetinib will also be conducted and submitted in the NDA.

- With the proposal to include summary safety data from patients treated in the Expanded Access Program as Council for International Organizations of Medical Sciences (CIOMS) II line listings cross-referenced to CIOMS I detailed case reports with a discussion included in the Summary of Clinical Safety.

- With the proposal to present exposure, AE, laboratory, vital sign, cardiac function, and ophthalmological safety analyses for the pediatric pooled group and pediatric subgroups, and to analyze AEs of special interest (AESIs) by the pooled pediatric and pooled adult single agent databases.

- With the plan that AZ will conduct and submit subgroup safety analyses for patients who received all their study-related evaluations at one of the four SPRINT clinical sites and for patients who had non-re-staging visits at local centers in addition to descriptive safety analyses between NCI POB and non-NCI sites.

- With the plan to submit eCRFs for patients who have experienced AEs leading to death, SAEs, death from an AE, death related to PN, study drug discontinuation and premature withdrawal from study while on treatment or within 30 days from the last dose of selumetinib.

- With the proposed content for the 120-day safety update including 12 months of additional safety data from approximately 25 patients in SPRINT Phase II Stratum 1, the updated SPRINT Phase II Stratum 1 safety dataset, and narratives for any previously unreported deaths, serious AEs, AEs leading to dose modification or dose discontinuation. FDA stated that additional analyses based on the data submitted may be requested during the review.

FDA stated the following:

- AZ should include, as part of the summary of the patient's course during the study, a discussion of the individual patient's safety and tolerability of selumetinib (e.g., AEs, dose reductions or delays, reason for discontinuation, need for additional supportive care medications for treatment related side effects, etc.) to allow for an individual benefit:risk assessment.

- The open-label trial design limits interpretability of Clinical Outcome Assessment (COA) data, but also acknowledged the challenges of measurement in diseases that are rare and heterogeneous across patients and symptoms. As such, submitted COA data will be reviewed as part of the totality of data.

- AZ should provide information that a difference in tumor size of 20-30% is expected to be outside of the margin of error for tumor measurements in the NDA.

On March 29, 2019, FDA granted Breakthrough Therapy designation to selumetinib for the treatment of pediatric patients age 3 years and above with NF1 and inoperable PN that is causing significant morbidity. The designation was based on the ORR and DOR results of the SPRNT trial and supportive preliminary results for the clinical outcome assessments conducted during the study which suggested trends of improved strength and motor function and decreases in pain that correlated with reductions in tumor volume observed during selumetinib treatment.

Product

Selumetinib (AZD6244, ARRY-142886) is a protein kinase (MEK1/2) inhibitor. The drug product consists of HPMC capsules containing selumetinib hydrogen sulfate (b) (4) of vitamin E, polyethylene glycolsuccinate. Selumetinib is supplied as a capsule in 10 mg and 25 mg strengths (expressed as free base) for oral administration. The 10 mg capsules are white, opaque, (b) (4) hard capsule, banded and marked with "SEL 10" in black ink and the 25 mg capsules are blue, opaque, (b) (4) hard capsule, banded and marked with "SEL 25" in black ink. Selumetinib capsules are packaged in 75cc HDPE bottles with desiccant, (b) (4) screw closure and induction seal. The recommended storage conditions for selumetinib capsules is storage in their original packaging until use and at temperature (b) (4)

Pharmacology/Toxicology

The planned nonclinical program for selumetinib in the currently proposed indication includes pharmacology studies investigating the mechanism of action of the drug and proof of concept studies in mouse genetic models of endogenous NF1-mediated tumors; pharmacokinetic studies investigating the ADME and drug-drug interactions; GLP-compliant general toxicology studies in mice and monkeys of up to 6 months duration; *in vitro* and *in vivo* genotoxicity studies; and reproductive toxicology studies investigating effects on male and female fertility, embryofetal development, and pre-and post-natal development. AstraZeneca does not plan to conduct juvenile animal studies to support the current indication.

Clinical Pharmacology

AZ stated that the doses used in the SPRINT study are lower than the doses used in adult oncology patients as a flat dose of 75 mg corresponds to a BSA-adjusted dose of 42 mg/m^2 and 50 mg corresponds to 28 mg/m^2 assuming a typical adult BSA of 1.8 m^2. C_{max} and AUC at 50 mg in adults (1036 ng/mL and 3075 ng*h/mL, respectively) are slightly higher than in children receiving a dose of 25 mg/m^2 (886 ng/mL and 2520 ng*h/mL, respectively). T_{max} (~1 hour) and terminal half-life (~ 6 to 7 hours) are similar between adult and pediatric groups.

The phase 1 clinical pharmacology studies of selumetinib to be included in the NDA submission are listed in the table below.

Study ID/ Status/ Report type	Study description	Formulation / Study treatment	Patient population / No. patients on selumetinib[a] [No. patients in study[a]]
D1532C00066 Completed Full Clinical Study Report	Randomized, open-label, crossover study to compare the white (current Phase II) and blue (planned Phase III) capsule formulations of selumetinib Hyd-Sulfate	Selumetinib Hyd-Sulfate capsules (white and blue) Single oral dose of: Selumetinib 75 mg white capsule Selumetinib 75 mg blue capsule	Healthy males 27
D1532C00069 Completed Full Clinical Study Report	Randomized, open-label, crossover study to assess the effect of food on the PK of a 75 mg single oral dose of selumetinib	Selumetinib Hyd-Sulfate capsule Selumetinib 75 mg in fed and fasted state	Healthy males 34
D1532C00071 Completed Full Clinical Study Report	Double blind crossover of single oral dose selumetinib or placebo on QTc interval, using moxifloxacin as a positive control	Selumetinib Hyd-Sulfate capsule Selumetinib 75 mg Moxifloxacin 400 mg Selumetinib placebo	Healthy males 54
D1532C00077 Completed Full Clinical Study Report	Open-label PK and mass balance study of single oral dose [^{14}C]-selumetinib	Selumetinib Hyd-Sulfate capsule [^{14}C]-Selumetinib 75 mg 22.57 MBq (610 µCi)	Healthy males 6

Study ID/ Status/ Report type	Study description	Formulation / Study treatment	Patient population / No. patients on selumetinib[a] [No. patients in study[a]]
D1532C00078 Completed Full Clinical Study Report	Randomized, open-label, crossover study to assess the bioequivalence or relative bioavailability of process variants of selumetinib	Selumetinib Hyd-Sulfate capsule Selumetinib blue reference capsules Selumetinib blue capsules Variant 1 (free base variant) Selumetinib blue capsules Variant 2 (TPGS variant)	Healthy males 48
D1532C00080 Completed Full Clinical Study Report	Open-label study to assess the absolute bioavailability of a single oral dose of selumetinib with respect to an iv microtrace dose of [^{14}C] selumetinib	Selumetinib Hyd-Sulfate capsule Selumetinib 75 mg followed by [^{14}C] selumetinib 80 µg, administered as a 15-minute infusion using a syringe pump. The radioactive dose of the iv solution will be ≤37 kBq (1000 nCi).	Healthy males 12
D1532C00081 Completed Full Clinical Study Report	Open-label study comparing PK, safety and tolerability following a single oral dose of selumetinib to healthy volunteers and subjects with renal impairment	Selumetinib Hyd-Sulfate capsule Selumetinib 50 mg	Healthy males and females, and subjects with end stage renal disease 24

Study ID/ Status/ Report type	Study description	Formulation / Study treatment	Patient population / No. patients on selumetinib[a] [No. patients in study[a]]
D1532C00082 Completed Full Clinical Study Report	Open-label study comparing PK, safety and tolerability following a single oral dose of selumetinib to healthy volunteers and subjects with hepatic impairment	Selumetinib Hyd-Sulfate capsule Selumetinib 50 mg in subjects with normal and mild hepatic impairment; 50 or 25 mg in subjects with moderate hepatic impairment; and 20 mg in subjects with severe hepatic impairment	Healthy males and females and subjects with hepatic impairment 32
D1532C00083 Completed Full Clinical Study Report	Open-label study to assess the effect of CYP3A4 inhibitor itraconazole and CYP2C19 inhibitor fluconazole on the PK of a single oral dose of selumetinib	Selumetinib Hyd-Sulfate capsule Selumetinib 25 mg Itraconazole 200 mg BID Fluconazole 400 mg od on Day 1 followed by 200 ng od	Healthy males and females 26
D1532C00085 Completed Full Clinical Study Report	Open-label study to assess the effect of CYP3A4 inducer rifampicin on the PK of a single oral dose of selumetinib	Selumetinib Hyd-Sulfate capsule Selumetinib 75 mg Rifampicin 600 mg od (multiple oral doses)	Healthy males and females 22
D1532C00086 Completed Full Clinical Study Report	Open-label, dose escalation study to assess the safety, tolerability and PK of single oral doses of selumetinib	Selumetinib Hyd-Sulfate capsule Selumetinib 25, 35 or 50 mg	Healthy Japanese, Non-Japanese Asian and Indian males 72
D1532C00089 Planned	Open label, relative bioavailability and food effect randomized crossover study of new granule and capsule formulations of selumetinib.	Selumetinib Hyd-Sulfate capsule 50 mg Selumetinib granule formulation 25 mg	Healthy male volunteers aged 18 to 45 years (24 to be enrolled to ensure 20 evaluable subjects)

[a] Evaluable for safety population

BID twice daily; iv Intravenous; od once daily; PK Pharmacokinetic(s); QTc corrected QT interval; TPGS d-α tocopheryl polyethylene glycol 1000 succinate.

Clinical and Statistical

Disease Background

Plexiform neurofibroma arises from a germline mutation of the NF1 gene encoding the tumor suppressor protein neurofibromin 1, a GTPase-activating protein that regulates hydrolysis of RAS-GTP and functions as a potent inhibitor of the RAS pathway. NF1 mutations can be inherited or spontaneous and the resulting loss of neurofibromin is associated with elevated levels of activated RAS. Activated RAS results in the initiation of a cascade of signaling events, such as activation of RAF and MAPK, which lead to increased cell proliferation. Penetrance is 100%; if a patient has the NF1 mutation, the disease will generally manifest by age 20, although the diagnosis is usually made earlier (by school age) and expressivity is highly variable. Patients with NF1 have an increased risk of developing tumors of the central and peripheral nervous system including plexiform neurofibromas (27%), optic pathway gliomas (15-20%), pheochromocytomas (1%), and malignant peripheral nerve sheath tumors (MPNST; 5%). Surgery is the only standard treatment for plexiform neurofibroma; however, surgery is often not an option, or it is not curative because the number and location of the tumors may prevent complete resection and therefore many patients present with or develop inoperable

masses. Treating physicians focus on the management of the comorbidities and alleviating symptoms. Systemic therapies are presently reserved for the control or amelioration of symptoms (e.g., pain relief).

Clinical Studies Supporting the Selumetinib NDA
The primary safety and efficacy data supporting the planned marketing application for selumetinib in pediatric patients with NF-1-associated PN will be from the NCI-conducted SPRINT trial, an open-label, single arm, multi-center, dose-finding (SPRINT Phase I) with expansion phase (SPRINT Phase II) study of selumetinib in children ages 3 and above with NF1 and inoperable PN. AZ also proposes to use data from the ongoing NCI POB Natural History Study and the placebo arm of the completed NCI-sponsored Study 01-C-0222 as an external control for the PFS and time to progression (TTP) results from the SPRINT trial.

SPRINT Phase I
The dose finding component included 24 patients ages 3-18 years who enrolled and were treated at doses of 30 mg/m^2 (n=6), 20 mg/m^2 (n=12), or 25 mg/m^2 (n=6). The recommended dose was determined to be 25 mg/m^2 twice daily. Dose-limiting toxicities (DLTs) were Grade 3 cellulitis (n=1), Grade 3 urticaria (n=1), Grade 3 creatine kinase (CK) elevation (n=1), and Grade 3 asymptomatic decreased left ventricular ejection fraction (n=1). The median duration of exposure was 1,488 days (approximately 49 months). There were no deaths. Serious adverse events (SAEs) were observed in 21% of patients, three patients (13%) experienced AEs that led to discontinuation, and dose reduction occurred in 50% of patients (n=12, four reductions were from the 30 mg/m^2 dose level). Dose interruptions for AEs occurred in 71% of patients.

The reported ORR in patients treated during the dose-escalation phase was 68%. ORR was defined as the percentage of patients with confirmed complete response (CR) or partial response (PR). Response was measured using 3D volumetric MRI, and according to (Response Evaluation in Neurofibromatosis and Schwannomatosis) REiNS criteria which defines partial response (PR) as a 20% or greater decrease in tumor volume as compared to baseline, confirmed when observed again within 3 to 6 months. The images were centrally reviewed at NCI by a single reviewer.

SPRINT Phase II
The expansion phase of the trial is ongoing and includes two cohorts: Stratum 1 includes patients who have PN-related morbidity at enrollment (accrual complete; N=50) and Stratum 2 includes patients without significant PN-related morbidity at enrollment who are at risk for development of morbidity. Stratum 2 had enrolled 24 of the planned 25 patients at the data cut-off date. Selumetinib is administered at 25 mg/m^2/dose orally twice daily continuously for 28-day cycles. The primary endpoint is ORR measured via volumetric 3D-MRI according to REiNS criteria. The secondary endpoints are DOR, TTP, PFS, and determination of the effect of selumetinib on pain, functional outcomes depending on the PN location (vision, airway, motor, bowel/bladder or other morbidity), physical functioning, disfigurement, QOL, and safety and long-term tolerability. Patients

will have efficacy follow-up for up to five years from the last patient enrolled. The protocol includes long-term safety follow-up for seven years following initiation of treatment or 5 years after study drug discontinuation, whichever is longer.

AZ plans to use the patients enrolled in Stratum 1 of the expansion phase of SPRINT as the primary efficacy population. The median duration of treatment in this cohort was 722 days (approximately 24 months). The best ORR according to the "NCI central analysis" is 66% (95% CI: 51,79); all responses were partial. As of the June 2018 cutoff date, the ORR is 56% (95% CI: 0.41, 0.770). All patients with response were followed for at least 12 months from time of onset of response. Median DOR from onset of response was not reached. Of the 33 initial responders, two patients developed progressive disease and three patients converted to stable disease at the data cut-off date.

AZ conducted an independent central review (ICR) of the MRI volumetric response data from SPRINT Phase II Stratum 1. The ORR according to the ICR per REiNS criteria was 44% (95% CI: 30, 59). AZ reports that of the 33 patients with a confirmed PR by the NCI central analysis, there was agreement by ICR for 21 patients having a confirmed PR. Of the remaining 12 patients, three had unconfirmed PR and nine had stable disease by ICR. There was agreement between the NCI and ICR analyses that there were no patients with a best response of progressive disease.

Of the 50 patients who received selumetinib in SPRINT Phase II Stratum 1, there were no deaths, and SAEs were reported in 12% of patients. Twelve percent of patients had AEs leading to discontinuation of selumetinib. Selumetinib dose reduction was reported in 24% of patients. No safety data was provided for SPRINT Phase II Stratum 2.

NCI Natural History Study

NCI is conducting an NF1 Natural History study that began enrollment in 2008 and has accumulated data from 166 patients regarding the natural history of NF1-related PNs and associated morbidity. AZ proposes to use the results from the NCI Natural History Study as an external control for tumor growth as part of the efficacy evaluation of selumetinib in patients with PN. AZ has analyzed the data collected up to October 15, 2018. A total of 111 patients enrolled as of the data cut-off date underwent at least two evaluable PN volumetric MRI scans, and 92 of these patients are between the ages of three and 18 years.

Analyses of percentage change in PN volume from baseline over time were performed in the age-matched population (n=92) and in patients who were enrolled in both the Natural History study and SPRINT Phase II Stratum 1 (the Natural History subset; n=9). Ninety patients in the Natural History Study were followed up to the maximum SPRINT follow-up duration. The PN volume change from baseline in the Natural History Study using the latter cohort (n=90) ranged from 4% shrinkage per year to 148% growth per year. The PN volume change from baseline in the SPRINT Phase II Stratum 1 patients (n=50) ranged from 27% shrinkage per year to 19% growth per year. According to AZ, the adjusted mean annual growth rate was +21% (95%CI 16, 27) in the Natural History

Study and -17% (95% CI: 20, -13) per year in the SPRINT Phase II Stratum 1 study. The percentage of patients with PN progression was 87% in the Natural History Study age matched cohort (n=92) and 6% in the SPRINT Phase II Stratum 1 study (n=50).

Study 01-C-0222
Study 01-C-0222 is a multi-center, double-blinded, placebo-controlled, cross-over study of tipifarnib (R115777) in children and young adults (≥3 and ≤25 years old) with NF1 and unresectable, progressive PN with the potential to cause significant morbidity. The primary endpoint was TTP, measured by 3D-volumetric MRI analysis. AZ proposes to use the placebo arm from Phase A (first period of cross-over; N=29) of the study as an external control for PFS and TTP in patients from SPRINT Phase II Stratum 1. Based on the last evaluable MRI-assessment in Phase A, 23/29 (79%) of patients in the placebo arm had progressed. In the subgroup of patients in SPRINT with progressive PN at enrollment, the probability of remaining without progression at two years was 89% (95% CI 62, 97) compared with 21% (95% CI 8,38) in the placebo arm of the tipifarnib study.

FDA issued preliminary comments on June 26, 2019. AZ emailed a response document on June 27, 2019, with a follow-up submission to the IND on July 3, 2019.

SPONSOR QUESTIONS AND FDA RESPONSES

1. *Does the Agency agree that the efficacy (tumor response and clinical outcome assessments) data from SPRINT Phase II Stratum 1 supported with tumor response data from Phase I and compared to the tumor response data in NCI POB NF1 Natural History study, is sufficient to support an NDA in the proposed pediatric population?*

   FDA Response:
   FDA agrees that the efficacy data from SPRINT Phase II Stratum 1, including ORR, DOR, and COA results, could support filing of a marketing application for selumetinib for the treatment of pediatric patients with NF1 (b) (4)

   FDA acknowledges AZ's rationale for proposing to use the NCI response and DOR assessments as the primary efficacy analyses; however, FDA generally relies on independently reviewed results of tumor response in a single arm study.

   While FDA acknowledges the multifactorial nature of detected changes in COAs during the study, to demonstrate a favorable benefit:risk assessment for selumetinib in a benign condition in which tumor shrinkage will not be predictive of improved survival, there should be a general correlation between decrease in tumor volume and improvement in disease-related functional impairment, symptoms, or an improvement in disfiguring tumors, to make the ORR results

clinically relevant. The acute and long-term safety of selumetinib in the intended patient population will also be considered in the overall benefit:risk assessment.

FDA agrees with AZ's plan to conduct and submit a supportive efficacy analysis comparing the SPRINT Phase II Stratum 1 response results to the proposed external control data from the NCI POB NF1 Natural History Study. Response rate and DOR results from patients enrolled SPRINT Phase I and SPRINT Phase II, Stratum 2 should also be submitted as supportive efficacy analyses.

Discussion:
See AZ's response document dated June 27, 2019.

During the meeting, FDA stated that they did not object to the proposal to retain the NCI central analysis of ORR and DOR as the primary endpoint. However, as previously communicated, FDA generally considers the results of independent review of ORR and DOR to be most free of bias and therefore most relevant for inclusion in product labeling. FDA recommended that AZ provide, in the NDA, a rationale for their selection of the NCI central analysis of ORR and DOR as the primary efficacy analysis. AZ agreed.

Regarding AZ's proposal to exclude SPRINT Phase II Stratum 2 efficacy and safety data from the NDA submission, other than line listings of serious adverse events, FDA did not agree. FDA acknowledged that efficacy data from this cohort may be difficult to compare to the efficacy data from Stratum 1 due to shorter follow-up, but asked AZ to provide preliminary ORR and DOR data from Stratum 2 in the 90-day safety update. AZ agreed to submit this data with the 90-day safety update, including the raw and derived data, the data analysis program (in Module 5), and a written analysis of the results (in Module 2). FDA agreed that a formal interim CSR for Stratum 2 would not be required. AZ stated that they would not be able to provide safety datasets from Stratum 2 at the time of NDA submission; FDA agreed with AZ's proposal to provide SAE line listings as the only safety data from Stratum 2 that will be provided in the submission. FDA and AZ agreed that these line listings will be updated with the 90-day safety update.

2. *Does the Agency agree that the key pediatric safety data from SPRINT Phase II Stratum 1, supported by SPRINT Phase 1, are sufficient to support an NDA in the proposed pediatric population?*

FDA Response:
There is insufficient information in the meeting package to fully address this question. In a response to these preliminary comments, please provide clarification regarding the following items referenced in the meeting package:

a. "SAE data from other pediatric externally-sponsored research."

b. The "handwritten component" for safety narratives from patients enrolled in the SPRINT trial.

In addition to the proposed safety analyses, safety data from the 24 patients enrolled in SPRINT Phase II Stratum 2 should be included in the NDA. These data can be analyzed separately but should also be pooled with the other SPRINT safety data and any additional single agent selumetinib pediatric safety data to allow for identification of potential safety signals in the larger NF1 population and in the pediatric population.

In general, FDA expects a data cut-off of no longer than 6 months prior to NDA submission.

Discussion:
See AZ's response document dated June 27, 2019, and the meeting discussion for Question #1.

AZ clarified that the "handwritten component" for safety narratives from patients enrolled in the SPRINT trial is actually typed and under goes a quality control check by AZ.

3. *Does the Agency agree with the Sponsor's proposed content of the Day 90/120 safety update?*

FDA Response:
FDA agrees with the proposed content for the safety update report; however, these results should be submitted for the 74 patients who have received selumetinib during SPRINT Phase II (i.e., both strata) and not limited to the 50 patients in Stratum 1.

Discussion:
See AZ's response document dated June 27, 2019, and the meeting discussion for Question #1.

4. *Does the Agency agree with the proposed content/format for study level and pooled datasets in the NDA?*

FDA Response:
The proposed content and format for the SPRINT D1532C00057 Phase II Stratum 1 study data appear acceptable. FDA acknowledges that the datasets for additional supportive studies may not be CDISC compliant. However, FDA notes that well-documented and well-formatted data sets are essential for the timely review of an application, and that it is AZ's risk to submit raw datasets in a legacy data format instead of the CDISC format given this consideration. FDA strongly recommends submission of datasets using CDISC standards. If AZ

chooses to submit data in an alternative format, FDA encourages AZ to follow CDISC standards as much as possible. In addition, FDA encourages AZ to submit a mock dataset of the clinical data for FDA to comment on the proposed format and contents.

Discussion:
See AZ's response document dated June 27, 2019. During the meeting, FDA acknowledged that as the case report tabulation packages supporting the upcoming NDA submission are complete, mock packages are not available. FDA advised that AZ plan for a dataset walk-through meeting to be held following the Application Orientation Meeting (preferably the same day).

5. *Does the Agency agree with the proposed indication statement?*

FDA Response:
The proposed indication may be acceptable; however, the final indication will depend on review of the safety and efficacy data for all patients and relevant subgroups.

Discussion:
See AZ's response document dated June 27, 2019. There was no discussion during the meeting.

6. *Does the Agency agree with the Sponsor's proposal for content and timing of the complete NDA application?*

AstraZeneca plans to a request rolling submission for the proposed NDA. The NDA application is intended to be submitted in 2 parts. Part 1 (SN 0000) of the rolling NDA submission will contain the complete Nonclinical Modules 2.4, 2.6, and 4, along with additional bioanalytical reports that are referenced in the Nonclinical Summaries. Part 1 will also contain the complete Quality Modules 2.3 and 3. Part 2 (SN0001) of the rolling submission will include complete Clinical Modules 2.5, 2.7, and 5, along with Module 1 Labeling and Administrative, and will complete the NDA. The Request for Proprietary Name Review will be submitted following submission of the complete NDA application.

Table 1 Timing and content of rolling submission

Rolling Submission Part	Approximate Submission Timings	Common Technical Document (CTD) Section
Part 1 (SN 0000)	Late July 2019	Modules 2.4, 2.6, and 4 and bioanalytical reports Modules 2.3 and 3
Part 2 (SN 0001)	August 2019	Modules 1, 2.5, 2.7, and 5

In accordance with Agency guidance (*Guidance for Industry – Integrated Summaries of Effectiveness and Safety: location within the Common Technical Document, April 2009*), AstraZeneca proposes that the Summary of Clinical Safety will be split between Module 2 and Module 5 as follows:

The main textual component will be presented within the Summary of Clinical Safety (Module 2.7.4).

The supportive data (tables, figures and listings) and safety narratives will be presented in the Reports of Analyses of Data from More than One Study (Including Any Formal Integrated Analyses, Meta-Analyses, and Bridging Analyses) (Module 5.3.5.3).

FDA Response:
As long as the information requested by FDA in Questions #1, #2, and #3 is provided in the August submission, FDA agrees with the proposed schedule.

Please note that the Summary of the Clinical Safety should not be split between modules 2 and 5; only the Integrated Summary of Safety may be split, if appropriate, between Modules 2 and 5.

Please clarify exactly when AZ plans to submit a request for Proprietary Name Review.

Discussion:
See AZ's response document dated June 27, 2019. There was no discussion during the meeting.

7. *Does the Agency agree with the proposal for an Application Orientation Meeting in support of the NDA for selumetinib to occur shortly after the submission?*

FDA Response:
Yes. An AOM has been scheduled for September 20, 2019.

Discussion:
See AZ's response document dated June 27, 2019. FDA acknowledged AZ's request to reschedule the Application Orientation Meeting, as key team members are unavailable on this date due to the neurofibromatosis conference happening at that time in California. FDA agreed to reschedule the Application Orientation Meeting.

8. *Does the Agency agree with the Sponsor's assessment that NF1 PN meets the criteria for Rare Pediatric Disease as defined in Section 529(a)(3)?*

FDA Response:
There is a possibility that your product may qualify for a Rare Pediatric Disease Priority Review Voucher. If you are interested in pursuing this possibility, please refer to the draft Guidance for Industry, "Rare Pediatric Disease Priority Review Vouchers," (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf). Determination of whether an application qualifies for a Rare Pediatric Disease Priority Review Voucher is a review issue and determined during the review of an NDA or BLA.

Discussion:
See AZ's response document dated June 27, 2019. There was no discussion during the meeting.

9. *The Sponsor intends to submit a request for Rare Pediatric Disease Designation for selumetinib at the time of NDA application to designate the NDA as a "rare pediatric disease product application" and request that FDA award a pediatric rare disease priority review voucher at the time of NDA approval. Does the Agency agree?*

FDA Response:
See FDA Response's to Question #8.

Discussion:
See AZ's response document dated June 27, 2019. There was no discussion during the meeting.

ADDITIONAL FDA COMMENTS

10. FDA recommends that the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support the NDA application be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available at https://go.usa.gov/xn4qB). 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.

11. Address the following in the Summary of Clinical Pharmacology:

    a. What is the basis for selecting the doses and dosing regimen used in the trials intended 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.

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

c. What is the effect of selumetinib on the QT/QTc interval?

d. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?

e. What are the effects of food on bioavailability? What are the dosing recommendations regarding meals or meal types? Provide justification for these recommendations.

f. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

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

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

b. Provide the 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 minimum and maximum values as appropriate.

c. 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.

d. 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.

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

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

1) Standard model diagnostic plots.

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

3) Model parameter names and units in tables.

4) A summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

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

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

2) 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.

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

h. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to the Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and models submission guidelines.

13. Include the following in the QT study report:

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. Clinical protocol.

c. Investigator's brochure.

d. Annotated CRF.

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

f. 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.

g. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable).

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

i. Narrative summaries and case report forms for any:

1) Deaths
2) Serious adverse events
3) Episodes of ventricular tachycardia or fibrillation
4) Episodes of syncope
5) Episodes of seizure
6) Adverse events resulting in the subject discontinuing from the study

j. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com).

k. A completed Highlights of Clinical Pharmacology Table.

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://cardiac-safety.org/ecg-database/.

Discussion regarding items #10-13:
See AZ's response document dated June 27, 2019. There was no discussion during the meeting.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed:

- FDA referenced the prior agreements as described in the November 13, 2018, WRO letter and summarized in the Regulatory History above.

- FDA referenced prior agreements made regarding the contents of the CMC portion. See meeting minutes dated May 9 and October 6, 2014, under IND (b) (4). FDA references ICH Q11 regarding the justification that AZ will have to provide for their starting material selections.

- FDA agreed that the contents of the nonclinical portion described in the meeting package appear complete.

- FDA acknowledged AZ's agreement to provide the requested clinical pharmacology information in the FDA.

- FDA agreed that the clinical portion of the application will be considered completed upon receipt of data from SPRINT Phase 2 Stratrum 1, SPRINT Phase 1, the NCI natural history study, and the tipifarnib clinical study placebo arm as described above.

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

- A preliminary discussion was held on the need for a REMS and other risk management actions. It was concluded that there was no need for a REMS or other risk management actions.

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

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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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.
- 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.

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1 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08 4159.htm

2 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09 3307.htm

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

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

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*.[3]

[3] https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRe quirements/UCM332468.pdf

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

- Assessment Aid[5]

[4] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm61292 7.htm

[5] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm61292 3.htm

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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/

SHARON K SICKAFUSE
07/09/2019 11:40:15 AM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 122851
Request Receipt Date	January 30, 2019
Product	Selumetinib
Indication	Neurofibromatosis type 1 (NF1)-related plexiform neurofibroma (PN)
Drug Class/Mechanism of Action	Small molecule MEK 1/2 inhibitor
Sponsor	AstraZeneca
ODE/Division	OHOP/DOP2
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	March 31, 2019

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

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

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

   The proposed indication in the BTDR for selumetinib is for the treatment of pediatric patients aged 3 years and above, with neurofibromatosis type 1 (NF1) symptomatic and/or progressive, inoperable plexiform neurofibromas (PN). DOP2 recommends modifying the indication to be more consistent with the study population enrolled in the trial from which results have been submitted as clincal evidence to support the BTDR. The designation decision letter would therefore grant breakthrough designation to selumetinib for the treatment of pediatric patients aged 3 years and above, with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibroma (PN) that is causing significant morbidity.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

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

4. **Consideration of Breakthrough Therapy Criteria:**

a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?

☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

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

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

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

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

Deny Breakthrough Therapy Designation ☐

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf
[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

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

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

7. **A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.**
   - *Information regarding the disease and intended population for the proposed indication.*
   - *Disease mechanism (if known) and natural history (if the disease is uncommon).*

Disease Background

Neurofibromatosis type 1 (NF1) is an autosomal dominant, tumor predisposition disorder with an incidence of 1:3500 (>80,000 persons affected in the United States). NF1 is characterized by various cutaneous, neurological, skeletal, and neoplastic manifestations that develop throughout a person's life, and there are no standard treatment options available. Patients with NF1 have an increased risk of developing tumors of the central and peripheral nervous system including plexiform neurofibromas (27%), optic pathway gliomas (15-20%), pheochromocytomas (1%), and malignant peripheral nerve sheath tumors (MPNST; 5%) (Friedman 2002).

NF1-related PNs are benign nerve sheath tumors that grow along the length of nerves and often infiltrate multiple branches of a nerve. The tumors are composed of neoplastic Schwann cells that lack NF1 gene expression resulting in the absence of functional neurofibromin 1. Loss of neurofibromin, which normally functions to regulate RAS, is associated with elevated levels of activated RAS. Activated RAS results in the initiation of a cascade of signaling events through the RAS/RAF/MEK/ERK pathway resulting in increased cell proliferation. PNs can arise in various locations throughout the body and cause significant morbidity by disfigurement and by compression of vital structures. Orbital PNs can displace the globe and compromise vision; paraspinal tumors can compress the spinal cord and cause paralysis; PNs arising in the mediastinum may compress the trachea or great vessels; and tumors arising in the extremities can cause progressive neurologic deficit and pain (Korf 1999). The NCI NF1 natural history study has demonstrated that PNs appear to grow linearly over extended periods of time, with younger children having faster PN growth rates than older children. Spontaneous regression is rare. Of the 112 PNs evaluated during the NCI study, seven tumors showed a spontaneous but slow decrease in volumetric growth (mean decrease/year: 4.8%; range: 2.3-7.8%); however these PNs were found in older patients (age at max volume: median 17.6 years, range: 11.1 – 26.7 years) (Gross 2018) .

Surgery is the only standard treatment for PN; however, resection is not an option for many patients who present with or develop inoperable masses. Additionally, surgery is often not curative because the location of the tumors or the encasement of essential structures prevent a complete resection. There are no available systemic treatments. Treating physicians focus on the management of the tumor related functional comorbidities and symptoms (e.g., pain relief).

Selumetinib Mechanism of Action

Selumetinib is an oral mitogen activated protein kinase inhibitor and a specific inhibitor of MEK 1 and 2. AstraZeneca (AZ) contends that selumetinib inhibition of MEK, which lies downstream from RAS, can block the inappropriate signal transduction through the RAS/RAF/MEK/ERK pathway and arrest tumor cell proliferation and growth.

Relevant Regulatory History

On September 8, 2014, a Type B Pre-IND meeting was held among FDA, National Cancer Institute (NCI), and AstraZeneca to discuss the development program for selumetinib for pediatric patients with inoperable NF1-related PN based on preliminary clinical results from the ongoing NCI-sponsored Study 11-C-0161 (CTEP#8799; SPRINT): "A phase 1 study of the mitogen activated protein kinase (MEK) 1 inhibitor AZD6244 hydrogen sulfate (selumetinib sulfate) in children with NF1 and inoperable plexiform neurofibromas". This study was conducted under IND (b) (4). As of the data cutoff for this meeting, 24 patients had enrolled and 13 of the patients (55%) had experienced partial response (PR) defined as >20% tumor volume reduction using volumetric MRI analysis as recommended by the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) Collaboration. (See #10 for further details on the REiNS criteria). NCI also provided summary information from an ongoing NCI-sponsored prospective natural history study in 83 patients with NF1-related PN regarding growth patterns and clinical morbidities. NCI, with the support of AZ, proposed to amend the ongoing SPRINT study with the incorporation of a single arm expansion cohort to further investigate the safety and effectiveness of selumetinib in pediatric patients with NF1-related PN.

The proposed primary endpoint was radiographic response using REiNS criteria. The group also proposed to measure improvements in functional impairment and patient-reported outcomes (PROs); however, these endpoints had not been defined prior to the meeting. The following key topics were discussed:

- FDA stated that if the prospectively collected data from the ongoing NCI natural history study demonstrate a consistent tumor growth rate, evidence that spontaneous tumor regression does not occur, and demonstration that improvement or worsening in measurable functional impairments correlate with decreases or increases, respectively, in tumor volumetric changes of ≥ 20%, this information could be sufficient to establish the natural history of the disease such that observed effects during the proposed study could be attributed to the selumetinib treatment effect and not the natural history of disease.

- FDA stated that for the proposed 20% reduction in tumor volume to be considered clinically relevant, it will be essential to show that this change in volume is reliably accompanied by a detectable effect on physical function or other measures indicating that the patient's quality of life is improved. FDA acknowledged that the protocol could include multiple functional/cosmetic assessment instruments for supportive efficacy assessments due to various tumor locations (e.g., vision testing for orbital tumors, strength testing for spinal tumors, photography for disfiguring lesions, etc.) such that AZ will likely have more than one set of criteria incorporated into the protocol.

- FDA stated that given the rarity of the disease to be studied, lack of treatment alternatives, and the debilitating complications arising from progressive PN, and provided that the natural history of disease has been adequately established through the NCI natural history study, a single-arm, externally-controlled (NCI natural history study) trial could support an application seeking approval if the study demonstrates unequivocal evidence of an important treatment effect that results in improved physical function or other well-characterized signs or symptoms of progressive PN disease. In addition to demonstration of a clinically meaningful magnitude of response, the trial must also demonstrate that such responses are sufficiently durable, considering the long term survival of patients with PN.

On March 3, 2015, FDA held a teleconference with AZ to discuss a preliminary request for Breakthrough Therapy designation based on the response rate observed in the ongoing SPRINT trial. All 24 patients experienced a decrease in tumor volume compared to baseline. A total of 16 patients (67%; 95% CI: 45, 84) experienced a partial response (PR) (≥ 20% tumor volume reduction as per volumetric MRI analysis). FDA stated that the significance of a 20% volumetric decrease in tumors was unclear and that a request for BTD would be strengthened by more examples that showed a clear correlation between decrease in tumor volume with improvements in function, symptoms, or an improvement in disfiguring tumors.

On September 4, 2015, the SPRINT study under NCI-sponsored IND (b) (4) was amended to include the phase 2 expansion cohort discussed at the preIND meeting. The amended study included two groups within the expansion phase: Stratum 1 was for the enrollment of 50 patients with PN-related morbidity at enrollment and Stratum 2 was for the enrollment of 25 patients without significant PN-related morbidity at enrollment who are at risk for development of morbidity. The primary endpoint was objective response rate (ORR) according to MRI volumetric analysis using REiNS criteria. The results from patients enrolled in Stratum 1 are the focus of the BTDR.

On July 17, 2017, AZ submitted IND122851 with an open-label, single-arm, multicenter intermediate access study for patients between 2 and 18 years of age with NF1 who have inoperable, progressive, symptomatic PN and no available alternative treatments.

On November 2, 2017, a Type C meeting between AZ and FDA was held to discuss AZ's planned analyses for ORR, duration of response (DOR), safety, PROs and functional outcomes from the SPRINT trial in preparation for submission of a marketing application. FDA agreed that if the data from the NCI natural history study provided sufficient evidence that spontaneous tumor regression or spontaneous reductions in PN-related morbidities do not occur as part of the natural history of disease, the observed effects in the SPRINT trial could be reliably attributed to the selumetinib treatment effect. FDA also agreed that the planned descriptive analyses of the changes in the functional evaluations and PROs could be used as supportive data in characterizing the clinical benefit of selumetinib. FDA recommended an additional response analysis be conducted after all patients have prolonged follow-up to better characterize the ORR and durability of response. FDA also stated that the general expectation for imaging endpoints used in a single-arm trial intended to support approval is blinded, independent confirmation of the ORR and DOR results.

On July 18, 2018, a Type C meeting between AZ and FDA was held to discuss potential trial conduct and data quality issues based on AZ's conduct of quality assurance audits of the SPRINT trial sites and the proposed risk mitigation plans to ensure reliability of the data. FDA generally agreed that AZ's plans to address potential trial conduct issues appeared reasonable; however, FDA stated that whether the mitigation procedures can allow for full confidence in the data will be determined during review of the NDA.

On August 29, 2018, AZ submitted a preNDA meeting request. The final topline results for DOR were not available and FDA could not agree to the final content of the planned NDA submission. FDA instead granted a Type C guidance meeting and issued written responses to AZ's questions regarding the structure, format and content of the future selumetinib NDA submission. The following key agreements were made:

- FDA agreed with AZ's plan to analyze ORR according to the REiNS volumetric MRI response criteria based on a blinded, independent review of images, its own analysis of the NCI central review of tumor volume data to derive ORR and DOR, and the original central NCI assessment. FDA noted that the results of the independent review of ORR and DOR would likely be used as the primary regulatory analysis in the context of a single-arm trial.

- FDA agreed with the proposal to not pool the efficacy data from the phase 1 and 2 parts of the SPRINT study due to differences in design and patient characteristics; however, AZ will conduct the supportive efficacy analyses using SPRINT phase 1 results, and these analyses will be submitted and presented in a side by side summary in the Summary of Clinical Efficacy (SCE).

- FDA stated that AZ's plan to reference tumor volume data from the NCI NF1 Natural History study and the placebo arm from Part A of the NCI Study 01-C-0222 as external controls for tumor growth and for the efficacy

endpoints progression free survival (PFS) and time to progression (TTP), respectively is acceptable; however, these analyses will be considered exploratory.

- FDA stated that AZ's proposal for the analyses of functional evaluations and PROs based on the descriptive statistics and mixed model repeated measures (MMRM) appeared acceptable, but noted that the open-label trial design limits interpretability of COA data because of patient's (or parent/caregiver's) knowledge of treatment assignment, lack of a comparator, small sample size, and potential instrument limitations. Despite this, FDA acknowledged the challenges of measurement in diseases that are rare and heterogeneous across patients and symptoms and as such, all submitted COA data will be reviewed as part of the totality of data.

- FDA agreed with the proposal to submit individual patient reviews (IPRs) as supportive efficacy data. The reviews will include relevant photos (e.g., baseline and best response) and timepoints during treatment when the photos were collected. FDA advised that in each IPR, AZ include a discussion of how the change in the target function or symptom correlates with the radiographic response and the timing of response. FDA also requested that each IPR include a discussion of the patient's safety and tolerability of selumetinib (e.g., AEs, dose reductions or delays, reason for discontinuation, need for additional supportive care medications for treatment related side effects, etc.) to allow for an individual benefit: risk assessment.

- FDA generally agreed to AZ's proposals for planned safety datasets and analyses.

On November 20, 2018, a second preliminary BTD teleconference was held. FDA recommended that AZ submit a formal request for BTD based on the response rate and duration of response results from the ongoing SPRINT study. FDA recommended that AZ also provide a summary of the correlation between the COA endpoints and radiographic response as part of the overall benefit:risk assessment.

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

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

AZ considers durable ORR according to MRI volumetric analysis using REiNS criteria to be a clinically meaningful endpoint supporting the BTDR. AZ additionally measured the effect of tumor shrinkage on disease-related symptoms and functional impairments as secondary endpoints in SPRINT phase 2. The specific functional assessments performed for each patient were selected prior to initiation of selumetinib based on the PN location and the related morbidity. AZ states that pain and motor dysfunction were among the most common morbidities observed at baseline in patients enrolled in SPRINT Phase 2 Stratum 1 (reported in 56% and 66% of patients, respectively). The BTD request therefore summarizes preliminary data for target PN pain (using pain intensity and pain interference tools), and for motor function (using strength and range of motion testing).

Other potential PN related morbidities that were less common at enrollment were airway (32%), vision (20%), bowel/bladder (20%) and other (18%) functional impairments; these were monitored with various PRO (e.g., Bladder And Bowel Patient Questionnaire) and functional assessments (e.g., pulmonary function tests) during treatment. These results and photographic data (to assess change in disfiguring tumors during treatment) will be submitted in the IPRs as part of the NDA.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*

- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*

- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

DOP2 would generally accept durable ORR as an endpoint that is reasonably likely to predict clinical benefit (e.g., improved survival) for a product intended to treat a malignant solid tumor. However, for benign tumors, durable ORR is not predictive of a survival benefit and would only be clinically relevant if there is evidence of a correlative improvement in one or more disease-related symptoms or functional outcomes. Therefore, for the evaluation of a treatment effect in patients with inoperable and symptomatic PN, DOP2 would accept ORR as a primary endpoint if it is supported by reliable data showing a sustained improvement in physical function or an improvement in specific symptoms related to the PN that correlates with radiographic tumor volume reduction. DOP2 also considers a meaningful improvement in disfiguring tumors to be evidence of clinical benefit.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

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

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*

- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There are no FDA-approved systemic therapies for patients with inoperable PN. Off-label cytotoxic chemotherapy has generally not been used. The following table summarizes ongoing or completed studies of various products that have been or are being evaluated in patients with inoperable and progressive PN.

Product	Mechanism of Action	Sponsor or reference	Comments
Imatinib	TKI	Univ of Indiana/Novartis	Completed. 36 patients, (b) (4)
Sorafenib	TKI	NCI	Completed. Nine patients < 18 yo with progressive PNs enrolled. (b) (4)
Nilotinib	TKI	Univ of Indiana/Novartis	Completed. Six patients enrolled. No responses per RECIST.
Tipifarnib	farnesyltransferase (FTase) inhibitor (blocks RAS signaling proteins)	NCI	Completed. 62 patients 3-25 yo with progressive PN received tipifarnib or placebo. (b) (4) .

Product	Mechanism of Action	Sponsor or reference	Comments
PEG-interferon	Immune modulator	Univ of Pittsburgh/NCI	Completed. 82 patients enrolled in 3 cohorts based on tumor growth and presence of symptoms. (b) (4)
Pirfenidone	Antifibrotic, antiinflammatory	NCI	Completed. 36 patients 3-21 yo enrolled. (b) (4)
Sirolimus	mTOR inhibitor	NCI	Completed. 29 patients 3-18 yo. Primary endpoint TTP as compared to external control. (b) (4)
Everolimus	mTOR	Pierre Wolkenstein, France	Completed. 30 pediatric and adult patients enrolled. (b) (4)
PD-0325901	MEK inhibitor	Univ. of Alabama	Completed. Single arm study of 19 patients > 16 yo with progressive or symptomatic PN; (b) (4) .
Cabozantinib	TKI	Univ of Alabama	Ongoing. Planned enrollment of 40 patients. (b) (4)
Trametinib	MEK inhibitor	St. Justine's Hospital, Canada	Ongoing. Plans to enroll 46 patients < 25 yo with progressive PN (b) (4)
Binimetinib	MEK inhibitor	Univ of Alabama, PPNOC	Ongoing. Planned enrollment of 40 patients. (b) (4)

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

There are no other drugs being developed for NF1-related PN for which a BTDR has been submitted.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The primary data supporting the BTDR for selumetinib comes from the NCI SPRINT study: " A Phase I/II Study of the Mitogen Activated Protein Kinase Kinase (MEK) 1 Inhibitor Selumetinib (AZD6244; HYD Sulfate) in Children with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN)." AZ also references published results from the ongoing NCI Natural History study of NF1-related PNs as supportive information.

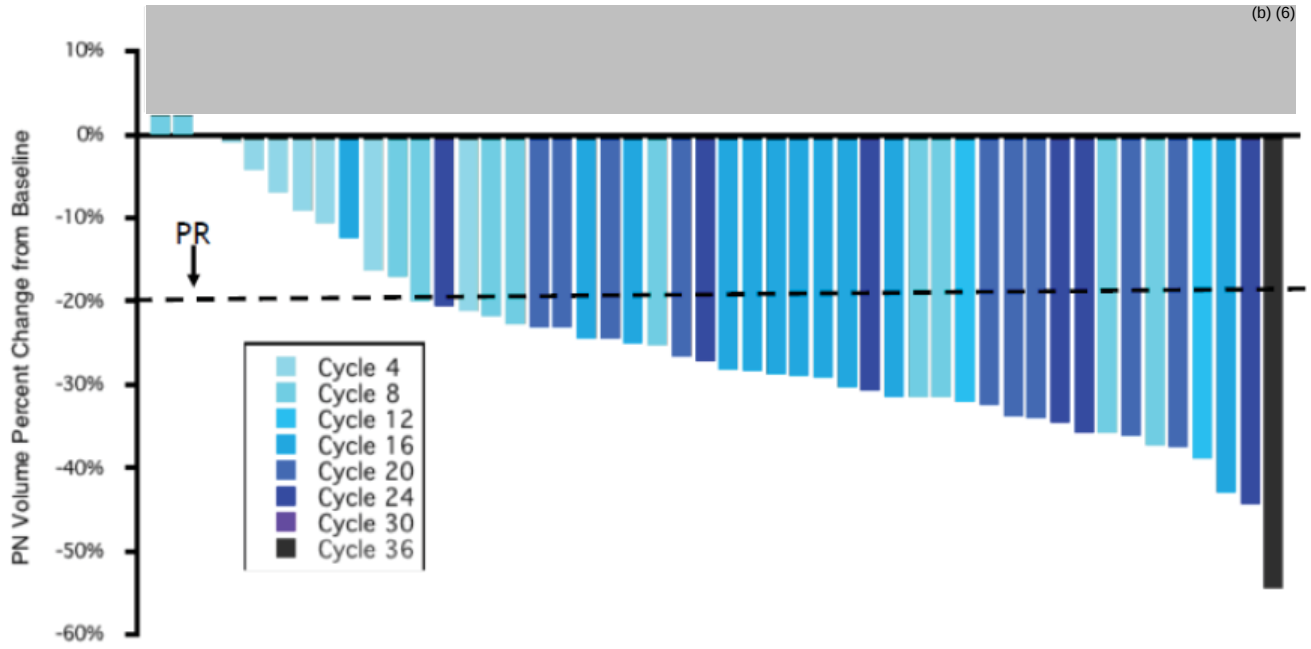
[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Study 11-C-0161 (CTEP#8799; SPRINT)
SPRINT is an open-label, single arm, multi-center, dose-finding with expansion phase study of selumetinib in patients 2 to 18 years old with NF1 and inoperable PN. Inoperable PN is defined in the protocol as PN that cannot be surgically completely removed without risk for substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN. The dose finding portion (SPRINT Phase 1) is complete and included 24 patients treated at doses of 30 mg/m2 (n=6), 20 mg/m2 (n=12), or 25 mg/m2 (n=6). The recommended dose was determined to be 25 mg/m2 twice daily continuous for 28 day cycles. The ORR according to centrally-read 3D volumetric MRI analysis using REiNS criteria in patients treated during this phase was 71%. The median DOR was 23 cycles (range: 6 to 42 cycles).

The expansion part of the study (SPRINT Phase 2) includes two cohorts, both of which have completed accrual: Stratum 1 enrolled patients with a documented significant PN-related morbidity, and stratum 2 enrolled patients with a PN that has the potential to cause a significant morbidity. Examples of lesions that cause or are considered high risk to cause significant morbidity per the protocol are head and neck lesions that could compromise the airway or great vessels, paraspinal lesions that can cause myelopathy, brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g., orbital lesions) or are significantly disfiguring, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions.

The results from SPRINT Phase 2 stratum 1 (N=50) are the focus of the BTDR. The primary endpoint was ORR via volumetric MRI analysis according to REiNS criteria. Tumor response was assessed at baseline and prior to Cycles 5, 9, 13, 17, 21, 25, and then every 6 cycles thereafter. As of the data cutoff of June 29, 2018, the confirmed ORR among the 50 patients treated in stratum 1 was 68%. Three additional patients had an unconfirmed PR at data cutoff. The median PN volume change from baseline for all patients at time of best response was -27% (– 55% to +2%). The following waterfall plot is copied from the BTD request briefing document.

Figure 1 **SPRINT Phase II Stratum 1 waterfall plot of best percentage change from baseline in target PN volume – NCI POB central review (REiNS)**



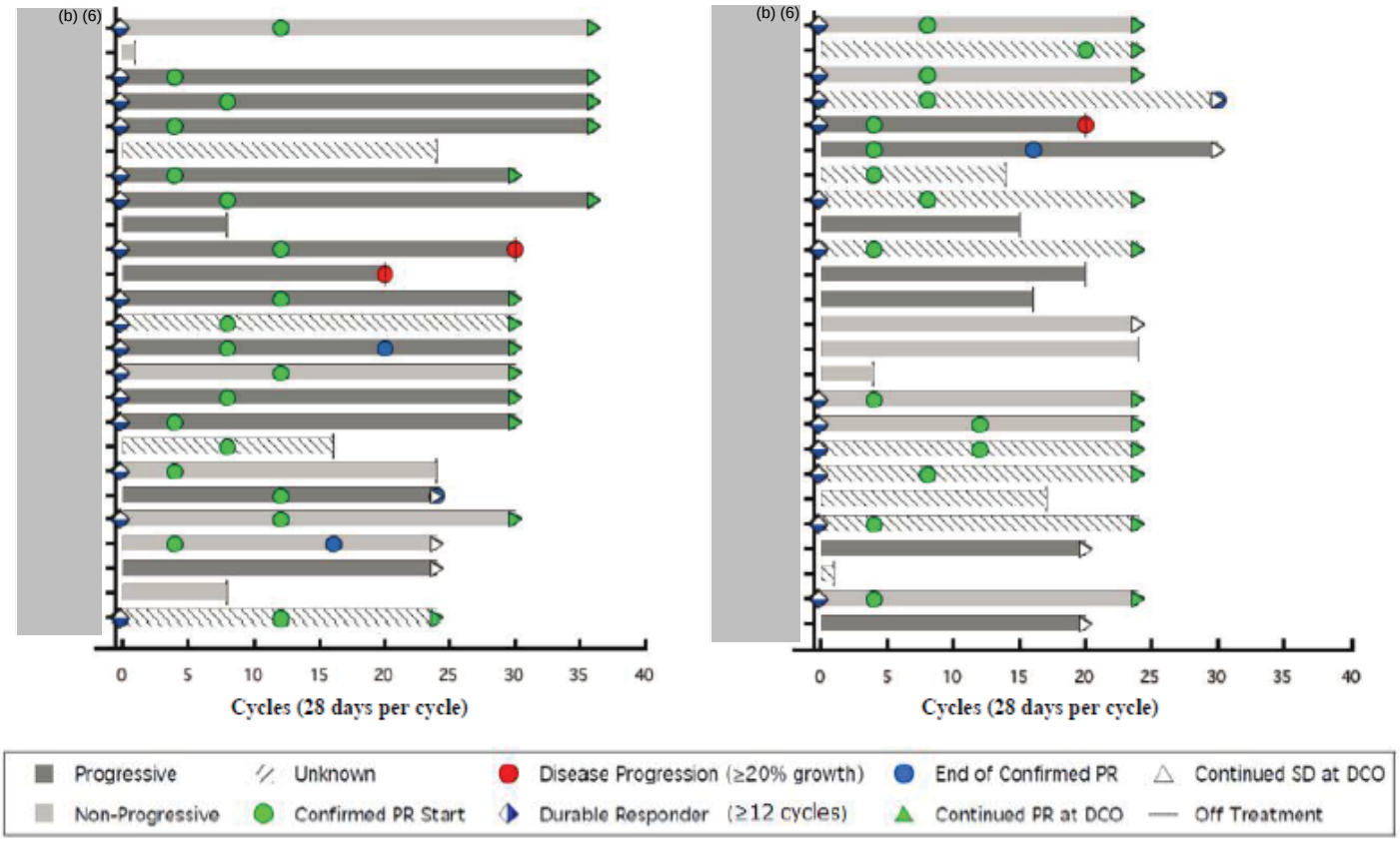
Best change in target PN volume is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction as assessed by central review.

NCI National Cancer Institute; PN Plexiform neurofibroma(s); POB Pediatric Oncology Branch; PR Partial response; REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis.

Source: Unpublished data from NCI POB

With regard to durability of the responses, at the data cut-off date, 28 (82%) of the 34 patients with confirmed PR had maintained an ongoing response for at least 12 cycles, and seven (21%) of the 34 had an ongoing response for at least 24 cycles. Disease progression was observed in 3 (6%) patients; therefore, the median DOR had not been reached. Thirty-three patients remained on-treatment at data cut-off. The following swimmer's plot shows the best response, time to onset of response and DOR for each patient treated in stratum 1.

Figure 2 SPRINT Phase II Stratum 1 Swimmer's plot of response status



COA Results

SPRINT Phase 2 stratum 1 includes the secondary objective of characterizing the effect of selumetinib on pain, quality of life, and general physical functioning. All patients (or parents/guardians depending on the age of the patient) were to complete the Pediatric Quality of Life Inventory (PedsQL; Varni, 2001) tool prior to cycles 5, 9 and 13. Pain was measured at baseline and pre cycles 5, 9, and 13 using the Numerical Rating Scale-11 (NRS-11) and the Pain Interference Index (PII) instruments. All patients with visible target PNs had serial photographic assessments. Additionally, the effect of selumetinib on specific functional outcomes was measured in subsets of patients that were grouped according to PN location and related baseline morbidity: orbital PN, airway PN, PN causing motor dysfunction, PN causing bowel and/or bladder dysfunction, PN affecting speech/swallowing, PN affecting hearing, and PN causing other dysfunction. To support the BTD request, AZ provided preliminary results for change in pain (using pain intensity and pain interference tools), and motor function (using strength and range of motion testing) from baseline during selumetinib exposure.

Pain

Of the 50 patients in Stratum 1, 33 patients were aged ≥8 years and completed the NRS-11 assessment of pain intensity at their baseline visit. Twenty-three of these 33 patients reported a level of tumor pain greater than 0 at baseline. NRS-11 scores were assessed over time from baseline to pre-Cycle 13 for 31 patients who completed the assessment at baseline and at least 1 post-baseline time point. AZ reports that at all time points following selumetinib initiation through pre-Cycle 13, there was a statistically significant decrease in median NRS-11 scores compared with baseline. Published studies have identified a decrease in 2 points on the NRS-11 scale as a clinically meaningful difference (Farrar et al 2001, Myrvik et al 2013, Salaffi et al 2004). AZ notes that of the 19 patients who had NRS-11 scores >0 at baseline and completed assessments at all time points up to and including the pre-Cycle 13 visit, 14 patients had a decrease in NRS-11 score of at least 2 points. Of these 14

patients with a self-reported improvement in pain intensity, 10 patients had achieved PR (at least 20% tumor volume reduction) by pre-Cycle 13.

For the pain interference evaluation, there were 20 patients ≥ 8 years old with self-reported PII scores at baseline and all time points up to and including pre Cycle 13 and 28 patients ≥5 years old with parent/guardian-reported PII scores at baseline and at all time points up to and including the pre-Cycle 13 visit. These 48 patients had a baseline PII score > 0 and the results indicate an improvement in the median score by the pre-cycle 13 assessment.

Table 6 SPRINT Phase II Stratum 1: assessment of pain interference

Outcome measure	Baseline	Pre-Cycle 13 visit
Pain interference: PII		
Patient self-reported, n=20[a]		
Median	1	0.5
Range	0.2 to 4.5	0 to 3.2
p-value[b]	<0.01	
Parent/guardian-reported, n=28[c]		
Median	1.8	0.3
Range	0.2 to 4.3	0 to 6.0
p-value[b]	<0.0001	

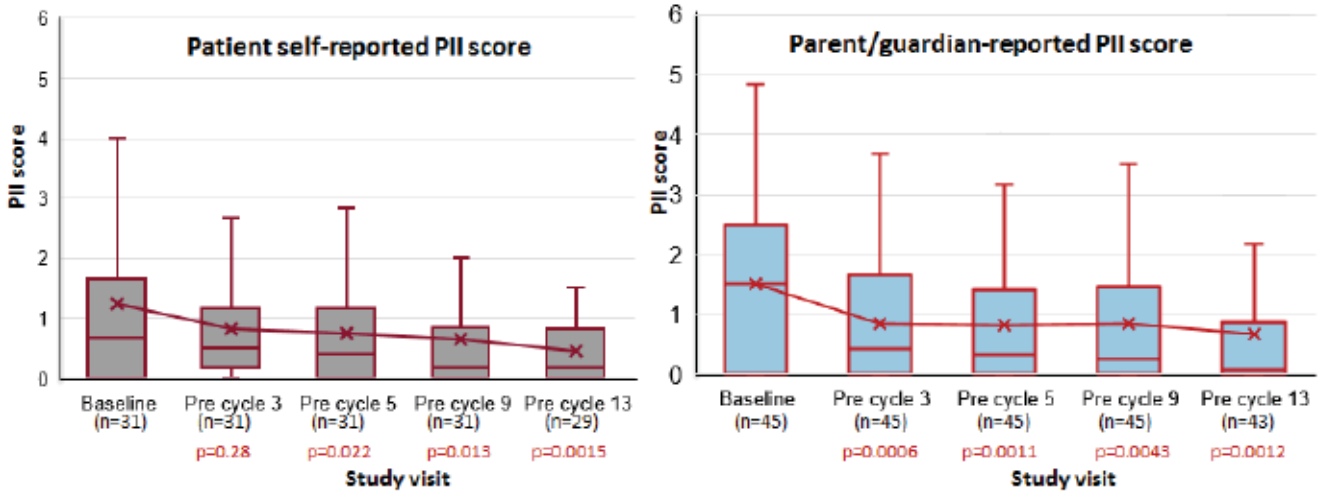
[a] Includes patients ≥8 years old with self-reported PII score data at baseline and at all time points up to (and including) the pre-Cycle 13 visit, and a baseline total PII score >0.

[b] Using the Wilcoxon signed rank test.

[c] Includes patients ≥5 years old with parent/guardian-reported PII score data at baseline and at all time points up to (and including) the pre-Cycle 13 visit, and a baseline total PII score >0.

PII Pain Interference Index.

Figure 5 SPRINT Phase II Stratum 1 patient self-reported and parent/guardian reported PII scores over time



Motor dysfunction

Of the 33 patients with motor dysfunction morbidities at baseline, 21 patients had strength score data at baseline and at all time points up to (and including) the pre-Cycle 13 visit, and an average strength score <5 at baseline. Twenty-six patients had range of motion score data at baseline and at all time points throughthe pre-Cycle 13 visit. Improvements in median scores between baseline and the pre-Cycle 13 visit were observed for both strength and range of motion outcome measures.

Table 7 SPRINT Phase II Stratum 1: assessment of motor function

Outcome measure	Baseline	Pre-Cycle 13 visit
Average strength of all muscle groups in the target PN body quadrant: MRC scale, n=21[a]		
Median	4.58	4.77
Range	1.84 to 4.83	2.13 to 5.00
p-value[b]	<0.001	
Range of motion (sum of the degrees of motion of all joints in the target PN body quadrant), n=26[c]		
Median	781	852
Range	345 to 1853	355 to 1895
p-value[b]	<0.001	

[a] Includes patients with strength score data at baseline and at all time points up to (and including) the pre-Cycle 13 visit, and an average strength score <5 at baseline.

[b] Using the Wilcoxon signed rank test.

[c] Includes patients with range of motion score data at baseline and at all time points up to (and including) the pre-Cycle 13 visit.

MRC Medical Research Council; PN Plexiform neurofibroma(s).

NCI Natural History Study

The NCI is conducting an NF1 Natural History study that began enrollment in 2008 and has accumulated data from more than 166 patients to allow characterization of the natural history of NF1-related PNs and the associated morbidities. The study plans to enroll up to 250 patients and will remain open for 10 years from the last patient enrolled. Patients have serial evaluations of their PN with volumetric MRI analysis as part of their participation in the study at least yearly until the age of 18 and at least every 3 years thereafter. PN growth rates are recorded. AZ included some results from the natural history study in the BTD Request as supportive information regarding tumor growth patterns and PN-related morbidity. The study has shown that typical PNs grow most rapidly in young children, and that the tumor growth rate decreases with increasing age. Data collected between February 2008 and December 2013 across 112 PNs in 95 patients demonstrated a growth rate of 12.4% per year (range: -8.5% to 246.7%), in patients with at least 1 year of follow-up data. Very few tumors showed any spontaneous regression (Gross 2018).

To support the notion that increases in tumor volume correlate with increasing morbidity, AZ references a published retrospective analysis of PN-related morbidities in patients enrolled in the Natural History study that suggests that there is considerable burden of PN-related morbidity in patients, starting at a very young age, and that these morbidities appear to worsen in the setting of increases in tumor volume. (Gross 2018). AZ provided the following results in the BTD request: Across 41 patients with 57 separate PNs included in the morbidity analysis, the median PN volume was 238 mL (range: 2.3 to 4895 mL). The median time between baseline and maximum volume assessments was 6.6 years (range: 0.5 to 12.6 years). Overall, 36 of 41 (88%) patients had at least 1 PN-related morbidity present at baseline including pain (n=21; 37% of total PN), followed by having had PN-related surgery (n=18) and motor dysfunction (n=11). At maximum volume assessment, 38 of 41 (93%) patients had at

least one PN-related morbidity present. With the exception of airways and vision, an increase was observed in all other types of morbidity at the time of maximum tumor volume. The study results also indicate that in the absence of surgical resection no symptomatic patients had improvement of their comorbidities.

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness .*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

DOP2 considers the data provided in the BTD request to be preliminary clinical evidence of a substantial improvement over the local control surgical options and supportive care therapies for inoperable and morbid PN. The effect sizes on ORR and DOR are substantially larger than those observed in clinical studies of other products evaluated in very similar study populations using the same volumetric response criteria. (see response to Question #9). Additionally, the preliminary results for the pain and motor dysfunction evaluations included in the BTDR suggest that there are trends of improved strength and motor function and decreases in pain that correlate with reductions in tumor volume during selumetinib treatment. Published results from the NCI Natural History study also suggest that increases in tumor volume correlate with increased patient morbidity and that symptomatic patients do not have improvement in tumor related morbidity when there is no change in tumor volume.

DOP2 acknowledges that COA results are necessary to support the clinical relevance of the ORR results given the benign nature of the condition, and that these data have limited interpretability in a single arm study. However, all patients in stratum 1 were required to have at least one baseline PN-related morbidity that could be measured by an appropriate COA tool during the study, and in the forthcoming NDA, AZ will be providing a detailed analysis of the correlation between tumor volume changes and changes in PN-related functional impairments or symptoms for individual patients and across groups of patients who underwent the same assessments. The detailed patient level data will likely inform the overall benfit:risk assessment for the intended population. AZ also plans to analyze the results from the NCI Natural history on PN growth patterns to support the overall efficacy evaluation of selumetinib in patients with PNs. DOP2 also carefully considered the MRI volumetric assessment of tumor volume and response and the safety of selumetinib in a pediatric population that would likely require chronic dosing during the review of the BTD request.

Response Evaluation

The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) Collaboration is an international academic group estabilished under the Children's Tumor Foundation in 2011 with the goal of achieving consensus across the NF community regarding the design and endpoints of clinical trials of new agents for the treatment of patients with NF-related tumors. The REiNS Tumor Measurement Group published standardized consensus recommendations for imaging response evaluation in clinical trials for benign NF tumors including PNs and vestibular schwannomas (Dombi 2013). Volumetric MRI analysis is the recommended method for evaluating radiographic changes in tumor size due to the complex shape, large size, and indolent growth of PNs. The goal of volumetric MRI analysis for response evaluation in NF is to

reproducibly detect small changes that would not be otherwise discernible. Based on close intraobserver and interobserver agreement of repeated volumetric MRI analyses, the group agreed on a 20% volume change to indicate a decrease or increase in tumor size. Therefore, the recommended volumetric response categories for benign NF tumors are defined as follows:

- Complete response (CR): Disappearance of the target lesion.
- Partial response (PR): Decrease in the volume of the target lesion by 20% or more compared to the baseline. The PR is considered unconfirmed at the first detection, confirmed when observed again within 3–6 months, and sustained when the response is maintained for 6 months or longer.
- Progressive disease (PD): Increase in the volume of the target lesion by 20% or more compared to baseline or the time of best response after documenting a PR. The appearance of new lesions or unequivocal progression of existing nontarget lesions is also considered PD.
- Stable disease (SD): Insufficient volume change to qualify for either PR or PD.

The first PN clinical trial using volumetric MRI analysis as the primary response assessment had a time to progression (TTP) primary endpoint and included a comparative analysis of response using 1-dimensional (RECIST), 2-dimensional (WHO), and 3-dimensional volumetric MRI assessments of PNs (Widemann 2014). The MRI volumetric analysis detected tumor progression (PN volume increase > 20%) much earlier than linear measurements. The REiNS group contends that detecting tumor progression substantially earlier limits time of exposure to potentially inactive or toxic agents and allows for completing trials more rapidly. The REiNS criteria has therefore been used in most recent studies of drugs being evaluated for the treatment of patients with PNs including NCI-sponsored multicenter trials of tipifarnib, pirfenidone, sorafenib, and pegylated-interferon. The volume reductions or increases correspond to much smaller changes in 1-D, or 2-D measurements. The following table was copied from the AZ briefing document submitted for the Type C meeting held on November 2, 2017.

Table 3: Comparison of 1-, 2-, and 3-dimensional response criteria

Response Criteria	RECIST Diameter, 2r	WHO Product, $(2r)^2$	NF1 PN trials Volume, $4/3\Pi r^3$
Disease progression (Increase)	20	44	73
	12	25	40
	6	13	20

Shaded areas show current criteria used to define disease progression by RECIST, WHO, and the ongoing NF1 phase II trials

DOP2 notes that AZ will be submitting an exploratory analysis of the SPRINT study using RECIST to measure ORR. These analyses will be conducted by (b) (4) and are not currently available.

Safety

DOP2 reviewed the summary safety data presented in the briefing document as part of the benefit:risk assessment of selumetinib in pediatric patients with inoperable PN. In SPRINT Phase 1, dose-limiting toxicities (DLTs) included Grade 3 cellulitis (n=1), Grade 3 urticaria (n=1), Grade 3 creatine kinase (CK) elevation (n=1), and Grade 3 asymptomatic decreased left ventricular ejection fraction (n=1). Patients

enrolled in Phase 2 Stratum 1 received a median of 28 cycles of selumetinib. The most frequent adverse events of any grade included CK elevation; gastrointestinal toxicities (including abdominal pain, diarrhea, constipation, nausea, vomiting, anorexia, oral mucositis, sore throat, and dry mouth); acneiform rash; and maculopapular rash. Most AEs were Grade 1-2 in severity. Four patients (8%) in SPRINT phase 2 stratum 1 discontinued study treatment for AEs considered possibly related to selumetinib. The overall safety profile appears to be consistent with the MEK inhibitor drug class.

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

☒ GRANT :

Provide brief summary of rationale for granting:

There are no systemic therapies approved for patients NF1 related PNs who have inoperable tumors. Although surgical resection is the standard of care, surgery is usually not curative as most PNs can not be completely resected due to infiltrative growth patterns and proximity to vital structures. Further, many PNs are inoperable at initial presentation. NF1-related PNs often cause disfigurement in addition to functional impariments and progressive pain. In some cases, the tumors can be life threatening via compression of the trachea or great vessels. DOP2 considers the effect size on durable response rate according to MRI volumetric analysis in patients with inoperable and morbid PNs to be preliminary evidence of a substantial improvement over available local control treatment options. The trends noted in the subset of patients who had pain and motor dysfunction at trial entry and who underwent pain and motor dysfunction assessments during selumetinib treatment are considered supportive of the radiographic response data in characterizing the clinical benefit of selumetinib in patients with inoperable and morbid NF1 related PN.

☐ DENY:

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

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

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

DOP2 has met with AZ multiple times to discuss the selumetinib development program in PN. DOP2 and FDA's Clinical Outcome Assessments Staff have additionally provided advice to AZ regarding the design and endpoints of SPRINT and the proposed analyses that will be included in the future NDA. DOP2 will continue to be available to AZ for regulatory guidance to facilitate the development program for selumetinib in this rare and morbid disease.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

1. Dagalakis U, Lodish M, Dombi E, et al: Puberty and plexiform neurofibroma tumor growth in patients with neurofibromatosis type I. J Pediatr 2013;164:620-4.

2. Dombi E, Ardern-Holmes SL, Babovic-Vuksanovic D, et al: Recommendations for imaging tumor response in neurofibromatosis clinical trials. Neurology 2013; 81:S33-40

3. Dombi E, Baldwin A, Marcus LJ, et al. Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas. N Engl J Med. 2016;375(26):2550–2560.

4. Friedman JM, Neurofibromatosis 1: clinical manifestations and diagnostic criteria. Journal of child neurology 2002;17:548-54; discussion 571-2, 646-51.

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

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

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

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

Revised 10/3/18/M. Raggio

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

/s/

DENISE A CASEY
03/21/2019 03:07:43 PM

SUZANNE G DEMKO
03/21/2019 03:22:39 PM

ASHLEY F WARD
03/22/2019 03:17:20 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 112851

MEETING MINUTES

AstraZeneca Pharmaceuticals LP
Attention: Elinore Mercer, Ph.D., RAC
Regulatory Affairs Director
1 MedImmune Way
Gaithersburg, MD 20878

Dear Dr. Mercer:

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

We also refer to the November 2, 2017, meeting between representatives of your firm and the FDA to discuss the development plans for selumetinib for the treatment of children and adolescents aged 3 and above with symptomatic and/or progressive neurofibromatosis-1 (NF-1)-related plexiform neurofibromas.

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, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	Other; Clinical
Meeting Date:	November 2, 2017
Application Number:	IND 122851
Product Name:	Selumetinib
Indication:	Treatment of children and adolescents aged 3 and above with symptomatic and/or progressive neurofibromatosis-1 (NF-1)-related plexiform neurofibroma
Sponsor/Applicant Name:	AstraZeneca Pharmaceuticals LP
Meeting Recorder:	Sharon Sickafuse

FDA ATTENDEES
Office of Hematology and Oncology Products
Paul Kluetz, M.D

Division of Oncology Products 2
Meredith Chuk, M.D.
Patricia Keegan, M.D.
Sharon Sickafuse, M.S.

Office of Biostatistics
Division V
Lisa Rodriguez, Ph.D.
Umaporn Siangphoe, Ph.D.

SPONSOR ATTENDEES
AstraZeneca, LP
Hesham Abdullah, MD, MSC; VP, Regulatory Affairs, Oncology
Gabriella Mariani, MD; Medical Science Director
William Bushnell, MS; Senior Director, Biometrics
Tracy Cunningham, MD; Clinical Head, Late Development Projects
George Kirk, PhD; Global Medicines Lead
Ali Khalil, MD; Patient Safety Physician
David Carlile, PhD; Dr. Pharmacology
Carol McConnell, BPharm, Dip Reg Affairs; Global Regulatory Lead
Elinore Mercer, PhD; US Regulatory Lead

National Cancer Institute
Andrea Gross, MD; Pediatric Oncology Fellow, POB
Brigitte Widemann, MD; PI for SPRINT, and Chief, POB
Andrea Baldwin, PNP; Clinical Nurse Practitioner, POB
Eva Dombi, MD; Research Biologist, SPRINT
Marielle Holmblad, RN; Clinical Research Nurse
Seth Steinberg, PhD; Senior Investigator, Biostats and DM
Janet Therrien, RHIT, CTR; Data Manager, POB
Trish Whitcomb, RN; Clinical Research Nurse, POB
Pam Wolters, PHD; Staff Scientist, SPRINT

Cancer Therapy Evaluation Program
Austin Doyle, MD; Medical Officer

Merck & Co, Inc.
Linda Gustavson, PhD; Ex. Dr. Global Regulatory Affairs
Scot Ebbinghaus, MD; Ex. Dr. Clinical Research
Scott Diede, MD, PhD; Senior Clinical Dr., Oncology Clinical Research

BACKGROUND
On July 5, 2017, AstraZeneca submitted a request (SDN 6) for a Type C meeting to discuss the development program for selumetinib for the treatment of children and adolescents aged 3 and above with symptomatic and/or progressive neurofibromatosis-1 (NF-1)-related plexiform neurofibromas (PN). The key study in this program is Study 11-C-0161, "A Phase I/II Study of the Mitogen Activated Protein Kinase (MEK) 1 Inhibitor Selumetinib in Children with Neurofibromatosis Type I and Inoperable Plexiform Neurofibromas (SPRINT)," sponsored by the Cancer Therapy Evaluation Program (CTEP) under an NCI IND. The meeting package was submitted on September 28, 2017, as SDN 11.

Selumetinib (AZD6244, ARRY-142886) is an oral protein kinase (MEK1/2) inhibitor, licensed for development by AstraZeneca from Array BioPharma. As of January 31, 2017, approximately 3,451 patients with cancer have received selumetinib. Selumetinib is being developed as a treatment for pediatric patients with NF1-related PNs and low-grade gliomas in collaboration with Cancer Therapy Evaluation Program (CTEP/NCI). Selumetinib is also currently being evaluated for differentiated thyroid cancer and NF1-related PNs in adults.

Regulatory History

On September 8, 2014, a Type B (Pre-IND/EOP1) meeting was held between FDA and AstraZeneca to discuss the development program for selumetinib for pediatric patients with inoperable NF1-related PN and to share the preliminary clinical information from the ongoing NCI-sponsored SPRINT trial.

On March 3, 2015, FDA held a teleconference with AstraZeneca regarding a preliminary request for breakthrough therapy designation based upon response rates from 24 patients from the SPRINT trial.

- All 24 (100%; 95% CI: 86, 100) patients experienced a decrease in tumor volume compared to baseline.
- Sixteen patients (67%; 95% CI: 45, 84) achieved a partial response (PR) (≥ 20% tumor volume reduction as per REiNS criteria volumetric MRI analysis); 9 (38%) had a sustained PR >6 months and 3 (13%) > 12 months.

FDA stated that the significance of a 20% volumetric decrease in tumor was unclear and that a request for breakthrough therapy designation would be strengthened by more examples that showed a clear correlation between decrease in tumor volume with improvements in function, symptoms, and/or cosmesis.

On July 17, 2017, AstraZeneca submitted IND122851 with an open-label, single-arm, multicenter intermediate access study for patients between 2 and 18 years of age with NF1 who have inoperable, progressive, symptomatic PN and no available alternative treatments. The trial is to enroll approximately 50 patients.

Nonclinical

The planned nonclinical program for selumetinib in the currently proposed indication includes pharmacology studies investigating the mechanism of action of the drug and proof of concept studies in mouse genetic models of endogenous NF1-mediated tumors; pharmacokinetic studies investigating the ADME and drug-drug interactions; GLP-compliant general toxicology studies in mice and monkeys of up to 6 months duration; *in vitro* and *in vivo* genotoxicity studies; and reproductive toxicology studies investigating effects on male and female fertility, embryofetal development, and pre-and post-natal development. AstraZeneca does not plan to conduct juvenile animal studies to support the current indication.

Clinical and Statistical

SPRINT Trial

The SPRINT trial is an open-label, single arm, multi-center study of selumetinib in children ages 3 and above with NF1 and inoperable PN. The dose-finding component is completed.

Dose-finding component

A 3+3 design was used to determine the MTD and the recommended dose of selumetinib with the dose-escalation schema in Table 1.

Table 1. Dose escalation schema

Dose Level	Dose (mg/m^2/dose q12h)	Equivalent fixed adult dose (mg)*	% change
-1**	12	22	40 ↓
1	20	36	-
MTD 1.5***	25	45	25 ↑
2	30	54	50 ↑
3****	40	72	33 ↑
4	50	90	25 ↑

Source: Table 1 in the statistical analysis plan v.3
* Based on body surface area (BSA) of 1.8 m^2,
** If MTD is exceeded at dose level 1 then the subsequent dose level will be -1 corresponding to a 30% dose reduction
*** This dose level is added after determining 20 mg/m^2/dose as the MTD to harmonize pediatric dosing with the MTD of 25 mg/m^2/dose determined in the Pediatric Brain Tumor Consortium (PBTC) study for low grade gliomas (Banerjee, et al., 2017)
**** Approximately equivalent to the adult MTD (75 mg/dose)

The primary endpoint was determination of the MTD and recommended dose for further investigation; secondary endpoints were growth rate of PNs via volumetric MRI, toxicity profile, and adherence. PNs were monitored by volumetric 3D-MRI analysis at baseline and at the end of cycles 5 and 10 and then after every 6 cycles.

Results

For the dose finding component, 24 patients ages 3-18 were treated: 6 patients at 30 mg/m^2, 12 patients at 20 mg/m^2, and 6 patients at 25 mg/m^2. The recommended dose was determined to be 25 mg/m^2 twice daily. Dose-limiting toxicities (DLTs) were: Grade 3 cellulitis (n=1), Grade 3 urticaria (n=1), Grade 3 creatine kinase (CK) elevation (n=1) and Grade 3 asymptomatic decreased left ventricular ejection fraction (n=1). The most frequent adverse events of any grade included CK elevation; gastrointestinal toxicities (including abdominal pain, diarrhea, constipation, nausea, vomiting, anorexia, oral mucositis, sore throat, and dry mouth); acneiform rash; and maculopapular rash.

As of July 31, 2017, 17 patients remained on study and 15 were on treatment. The median number of cycles per patient is 44 (range 6 - 74). Nine patients discontinued treatment: disease progression (n=1), toxicity (n=2), completed 2 years on study with stable disease (n=1), patient preference (n=1), refused further treatment (n=1), side effects (n=1), deemed in the patient's best interest (n=1) and loss of tumor response (n=1).

A partial response was defined as a tumor volume decrease from baseline of at least 20% for at least 4 weeks. Decreases in PN volumes (median: -31%, range: -5.8% to -47.7%) were observed in all patients, with a confirmed partial response rate of 71%. Partial responses to selumetinib were observed in 5 of 9 (56%) patients with documented progressive tumors at enrollment, in 4 of 6 (66.6%) patients with growing tumors, who did not meet criteria for progressive disease by

protocol definition, in 2 of 2 patients who were enrolled with stable tumors, and in 6 of 7 (86%) patients who were enrolled without prior volumetric data. The maximum response was reached after a median of 20 cycles (range 5 - 42). Responses have been maintained for a median of 23 cycles (range 6 - 42).

Activity-Estimating Component

For the activity-estimating portion of the trial, selumetinib is administered at 25 mg/m^2/dose orally twice daily continuously for 28 day cycles. Patients were enrolled in 1 of 2 strata based on the presence (Stratum 1) or absence (Stratum 2) of PN-related morbidity defined as presence of pain, difficulty in physical function, or disfigurement.

The primary endpoint is objective response rate (ORR) (confirmed completed response [CR] and partial response [PR]) via volumetric 3D-MRI in stratum 1 after all patients have 12 months of follow-up. The secondary endpoints are ORR, duration of response (DOR), PN growth rate, patient-reported outcomes (PRO), time-to progression (TTP) and progression-free survival (PFS) in patients in stratum 1 and 2. PN will be monitored at baseline and every 4 cycles until cycle 25, then after every 6 cycles thereafter.

PRO and functional outcomes will be evaluated throughout the study, but the primary analysis focuses on 1 year of follow-up. Functional morbidity measures are administered at baseline and follow-up using these instruments: Peds QL (self and parent reports) for general health- related quality of life (HRQoL); the numerical rating scale-11 (self report) for pain intensity; pain interference index (parent report) for pain interference; global impression of change scale (self and parent report) for global impression of change; serial photography/videography for disfigurement; PN symptom checklist for general symptoms. The physical functioning analysis subgroups will be based on PN locations (orbit, airway, motor, bowel/bladder). Correlation between tumor responses and change in patient/parent functional outcomes will be explored.

A list of functional morbidity and PRO assessments are presented in the tables below.

Table 12 **SPRINT study (Phase II): list of functional morbidity assessments for patients with PN related morbidity**

Morbidity	NCI Phase II SPRINT Protocol Appendix[a]	Measurement
Disfigurement	IV	Serial Photography and Videography
General symptoms	V	PN Symptom Checklist
Vision	VII	Visual Acuity Testing
	VII	Exophthalmometry
Airway	VIII	Polysomnography (Sleep Study)
	VIII	Spirometry (Pulmonary Function Testing)
	VIII	Impulse Oscillometry (Pulmonary Function Testing)
Airway + Motor	IXa	Six Minute Walk Test
Motor	IXb	Strength (Manual Muscle Testing)
	IXc	Range of Motion
	IXd	Leg Length Discrepancy
	IXe	Grooved Pegboard
Bowel/Bladder	X	Bowel/Bladder Questionnaire
Speech/Swallow	Xa	Speech Pathology Assessment
Audiometry	N/A	Audiology Assessment

[a] See the NCI SPRINT study protocol in Appendix B.
Each patient receives baseline and serial assessments of morbidities relevant to the location of their PN.
N/A Not applicable; NCI National Cancer Institute; PN Plexiform neurofibroma.

Table 13 **SPRINT study (Phase II): list of PRO assessment measures**

Domain	Measurement
Pain intensity	Numeric Rating Scale-11 (self-report)
Pain interference	Pain Interference Index (self-report)
	Pain Interference Index (parent-report)
Quality of life	PedsQL Generic Acute Form (self-report)
	PedsQL Generic Acute Form (parent-report)
Physical functioning	PROMIS Physical Functioning Mobility and Upper Extremity Scales (self-report)
	PROMIS Physical Functioning Mobility and Upper Extremity Scales (parent-report)

PedsQL Pediatric Quality of Life InventoryTM; PROMIS Patient-Reported Outcomes Measurement Information System.

(source: AstraZeneca meeting package)

Statistical considerations

Planned enrollment for the Phase 2 portion of the trial is 80 patients. Fifty patients were needed in Stratum I to detect the difference between a null hypothesis response rate of 15% and an alternative hypothesis response rate of 36% with a nominal one-sided 2.5% significance level and 90% power. Assuming 14 or more responses out of the 50 patients (a response rate of ≥25%), the lower limit of the exact two-sided 95% confidence interval for the response rate is 16.2% or greater. A response rate of ≥25% (19 or more response in 75 patients) is associated with a lower bound of a two-sided 95% CI which exceeds 15.0%.

Results

The activity-estimating portion of the trial is ongoing. As of August 31, 2017, 92 patients have been treated on the SPRINT trial; 50 have been enrolled in Stratum 1. The data cut-off for the primary analysis for Stratum 1 occurred on August 17, 2017, and database lock is anticipated in late Q4 2017.

Information in the following table was provided by AstraZeneca at the request of FDA as a preliminary response analysis as of October 13, 2017.

Target PN volumetric response (N=50)	**Best response through C12 n (%) (95% CI)**	**Best response as of August 31, 2017 n (%) (95% CI)**
No restaging evaluation	2 (4) (0,14)	2 (4) (0,14)
Progressive disease	0 (0) (0,7)	0 (0) (0,7)
Stable disease	12 (36) (15, 40)	12 (24) (13, 38)
Confirmed partial response (cPR + sPR)	**24 (48)[1] (34, 63)**	**32 (64)[2] (49, 77)**

Abbreviations: cPR=continued PR documented within 3-6 months of unconfirmed PR; sPR=PR maintained ≥ 6 months

[1] An additional 11 patients had an unconfirmed PR

[2] An additional 4 patients had an unconfirmed PR

NCI Natural History Study

The National Cancer Institute (NCI) is conducting an NF1 Natural History study that began enrollment in 2008 and, as of July 25, 2017, has accumulated data from 166 patients regarding the natural history of NF1-related PNs and the associated morbidity. Patient characteristics from the natural history study are summarized below:

Baseline Demographics	**N=166**
Age at enrollment, years	
Median (range)	13.3 (0.3-45)
Duration of follow-up, years	
Median (range)	6.9 (0-9.4)
Sex, n (%)	
Male	98 (59)
Female	68 (41)
Number of patients with PN	149 (90)

A comprehensive analysis of PN growth rate and characteristics from serial MRIs with volumetric analyses was performed on 113 PNs in 95 patients. Of these 95 patients, 72 patients with 82 PNs had not received any PN-directed therapy during this time and therefore were included in the growth rate analysis presented below:

Table 4 NCI NF1 Natural History study: growth rate of PNs

	Patients with ≥1 year follow up	
	Untreated patients (n=72)	**All patients[a] (n=95)**
Number of PNs	82	113
	Median (range)	
Age at initial MRI, years	9.6 (0.7-40.2)	8.4 (0.7-40.2)
Initial PN volume, mL	331 (4-4895)	295 (4-4895)
Final PN volume, mL	561 (14-6513)	606 (14-6980)
Duration of follow-up, years	3.0 (1.0-12.9)	5.6 (1-14.2)
Growth rate[b], % per year	12.4% (-8.5% to 246.7%)	
Tumor volume % change[c], final - initial volume/year		13.9% (-5.8% to 252%)

Data from Akshintala et al Draft Manuscript (Appendix E).

[a] Treatments that patients in this analysis received during the course of the Natural History study included, but were not limited to: acutane; imatinib; interferon (pegylated); phenylacetate; phenylbutyrate; pirfenidone; sirolimus; sorafenib; thalidomide; tipifarnib; vinblastine; vinblastine/methotrexate; vincristine/carboplatin. Note: Not all of these treatments were directed at the PNs.

[b] Based on continuous data (measured as the slope of the curve of tumor volume over time).

[c] Based on non-continuous data ([final tumor volume – initial tumor volume]/number of years).

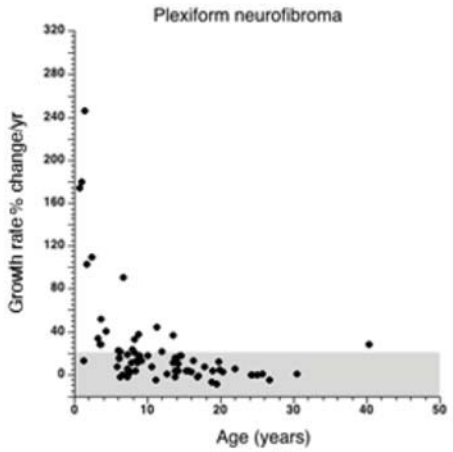
MRI Magnetic resonance imaging; NCI National Cancer Institute; PN Plexiform neurofibroma.

(source: AstraZeneca meeting package)

In the NCI NF1 Natural History study, typical PNs grew most rapidly in young children (Figure 2 below); the growth rate of typical PNs decreased with increasing age, with tumors in adult patients rarely growing ≥20% per year. Spontaneous PN shrinkage of >10% from the maximum volume was seen for 10 of the 113 PNs (8.8%) that were amenable for volumetric analysis (from 95 patients with ≥ 1 year follow-up). The maximum rate of spontaneous shrinkage seen in any of these PNs was 8.5% per year (range: 2.1% to 8.5% decrease per year). The median age for patients who had PNs that had spontaneous shrinkage of more than 10% from maximum volume was 19 years (range: 8.4 to 26.7 years). In untreated patients with typical PNs, followed for a median of 3.0 years (range: 1.0 to 12.9 years), there was a median growth rate of 12.4% per year (Figure 2).

Figure 2 **NCI NF1 Natural History study: growth rate vs age of typical PNs**

A



Data from Akshintala et al Draft Manuscript (Appendix E).
Note: Each dot represents 1 plexiform neurofibroma.

(source: AstraZeneca meeting package)

Response rate endpoint

The SPRINT trial measures tumor response using a non-standard response measurement (automated volumetric MRI analysis) recommended by the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) Collaboration. This method is currently used to centrally evaluate PN volume in multicenter, NCI-supported clinical trials for children with NF1 and PN. With this response measurement criteria, tumor progression is defined as an increase in tumor volume by ≥ 20% and tumor response is defined as a decrease in volume by ≤ 20%. The following table compares the volumetric analysis to other solid tumor response criteria.

RECIST 1D (2r)	WHO 2D (πr^2)	Volume 3D ($4/3\ \pi r^3$)
−30% PR[a]	−50% PR[a]	−66%
−7%	−14%	−20% PR[a]
6%	13%	20% PD[a]
12%	25% PD[a]	40%
20% PD[a]	44%	73%

(Dombi *et al*., Neurology 2013)

FDA emailed Preliminary Comments to AztraZeneca on October 30, 2017. On November 2, 2017, FDA received via email a response document which was submitted to the IND on November 15, 2017.

SPONSOR QUESTIONS AND FDA RESPONSES

1. *Does the Agency agree that the NCI Natural History study data provide an adequate characterization of the growth rate of NF1-related PNs in untreated NF1 patients to provide an appropriate comparison for the open-label, single-arm SPRINT study?*

   FDA Response:
   FDA agrees that the summary of the data from the NCI natural history study suggests that durable tumor shrinkage is likely due to treatment with selumetinib, rather than the natural history of the disease; however, FDA cannot determine whether the NCI natural history study results will provide an adequate characterization of NF1-related PN growth rate and associated morbidity until the data is submitted and reviewed. If these data provide sufficient evidence that spontaneous tumor regression or reductions in PN-related morbidities do not occur as part of the natural history of disease, the observed effects in the SPRINT trial could be reliably attributed to the selumetinib treatment effect. FDA recommends that AstraZeneca conduct its own analysis of the data from the NCI natural history study and provide a summary of these results at the time of the preNDA meeting.

   AstraZeneca Response:
   AstraZeneca considers that the analyses performed by NCI are robust and relevant to establish an adequate characterization of NF1-related PN growth rate as well as to document the presence of substantive morbidity in this population. AstraZeneca agrees to perform an analysis of the data from the NCI Natural History study to support the comparison to SPRINT. The final proposal will be presented to FDA at a Type C Structure and Format preNDA meeting, and these data can be presented and discussed at a Type B preNDA meeting as requested. Does the Agency agree?

   Discussion:
   FDA stated that this proposal was acceptable.

2. *Does the Agency agree that the current data from the NCI Natural History study support that reductions in PN-related morbidities are extremely rare for patients with stable or growing tumors?*

   FDA Response:
   See response to question #1.

   AstraZeneca Response:
   No separate discussion at the meeting is needed.

   Discussion during Meeting:
   See discussion under Question 1.

3. *Does the Agency agree that the prospectively defined secondary endpoints, including PROs and functional evaluations, in the Phase II Stratum 1 portion of the SPRINT study are appropriately selected to further characterize the clinical benefit of durable*

radiographic response (PN volume reduction) in children aged 3 and above and adolescents with symptomatic and/or progressive NF1-related PNs?

FDA Response:
While the selected secondary endpoints in the SPRINT study, including the PRO measures listed in Table 13 and the disease-related functional impairments listed in Table 12 of the meeting package appear reasonable, the reliability of the results of these assessments as supportive evidence of the clinical benefit of selumetinib in patients with symptomatic PN who experience radiologic objective responses during treatment will be determined during the application review. Note that the PROs and functional morbidity assessments are considered exploratory in this single-arm trial and are unlikely to support labeling claims. The protocol and statistical analysis plan (SAP) should include evaluation of compliance of data collection for each instrument (e.g., completion rates, definition of eligible patients [both self and parent reports], definition of patients who fill out the instruments, handling missing data).

AstraZeneca should include censoring rules for PFS in the protocol and SAP. For example, see censoring rules of cancer endpoints described in the FDA Guidance for Industry," Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics," at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf.

AstraZeneca Response:
AstraZeneca plans to summarize the missing data on a per-visit basis to demonstrate the completeness of data collection. AstraZeneca will include censoring rules for PFS similar to RECIST standards, for example, two or more missing scan visits and patients with no baseline scans. This information will be included in the next version of the SAP. No separate discussion at the meeting is needed.

Discussion during Meeting:
No discussion occurred.

4. *Does the Agency agree with the planned analyses to demonstrate response rate in children aged 3 and above and adolescents with symptomatic and/or progressive NF1-related PNs in the Phase II Stratum 1 portion of the SPRINT study?*

FDA Response:
The plan to demonstrate response rate in the target population is acceptable; however, the length of follow-up may not be adequate. See response to question 9.

AstraZeneca Response:
AstraZeneca acknowledges the FDA's response.

Discussion during Meeting:
Please refer to discussion for Question 9.

5. *Does the Agency agree that the planned descriptive analysis of the changes in the functional evaluations and PROs in the Phase II Stratum 1 portion of the SPRINT study, as described in the SAP, are appropriate to further characterize the clinical benefit of treatment with selumetinib in children aged 3 and above and adolescents with symptomatic and/or progressive NF1-related PNs*?

FDA Response:
FDA agrees that the planned descriptive analysis of the changes in the functional evaluations and PROs can be used as supportive data in characterizing the clinical benefit of selumetinib. However, the protocol and SAP should include the evaluation of compliance of data collection. See response to question 3.

AstraZeneca Response:
AstraZeneca acknowledges the FDA's response.

Discussion during Meeting:
FDA requested, and AstraZeneca agreed to provide, a prospective plan for analysis of functional and PRO data for FDA's review and comment. FDA noted that although the data are exploratory, the totality of the data provided in the NDA will be evaluated and that a prospective plan for analysis will be useful in assessing the strength of the analyses in support of the planned NDA.

6. *Does the Agency agree that the planned correlation analyses between the primary endpoint and the secondary functional and PRO endpoints are adequate to characterize a relationship between the documented effect of selumetinib in reducing tumor volume and improvements in symptomatic and functional measures relevant to children aged 3 and above and adolescents with symptomatic and/or progressive NF1-related PNs?*

FDA Response:
FDA considers the correlation analyses as exploratory analyses; however, these analyses can be used in considering the totality of the evidence supporting the efficacy of selumetinib in this patient population.

AstraZeneca Response:
AstraZeneca acknowledges and agrees with the FDA's response. No discussion is needed at the meeting.

Discussion during Meeting:
No discussion occurred during the meeting.

7. *Does the Agency agree that the clinical program for selumetinib, including 11 adult clinical pharmacology studies in conjunction with adult monotherapy studies, and data from the SPRINT pediatric study, form a sufficient safety database to support an NDA submission for selumetinib for the treatment of children aged 3 and above and adolescents with symptomatic and/or progressive NF1-related PNs?*

FDA Response:
The description of the proposed safety database appears adequate to support an NDA submission if there are no safety signals detected that are unique to the pediatric population that may not be adequately characterized by the relatively small number of pediatric patients who have received selumetinib. As mentioned during the September 8, 2014, preIND/EOP1 meeting, given that selumetinib is intended for chronic use in a pediatric patient population that has known increased lifetime risk for other medical comorbidities due to underlying NF-1, if the data collected in the timeframe proposed for long-term follow-up of patients demonstrates a safety signal of clinical importance (e.g., developmental disorders, risk for cardiac dysfunction, or ophthalmologic disorders), FDA recommends that AstraZeneca develop a program to track specific delayed or ongoing adverse drug reactions.

AstraZeneca Response:
AstraZeneca acknowledges and agrees with the FDA's response. No discussion is needed at the meeting.

Discussion during Meeting:
No discussion occurred during the meeting.

8. *Does the Agency agree that the proposed nonclinical package of completed and ongoing studies, including carcinogenicity studies, can support a NDA submission for selumetinib for the treatment children aged 3 and above and adolescents with symptomatic and/or progressive NF1-related PNs?*

FDA Response:
The proposed nonclinical package of completed and ongoing studies described in the meeting package, which includes carcinogenicity studies and a full battery of reproductive toxicology studies but not juvenile animal studies, appears sufficient to support filing of a future NDA. Whether the data from these studies are adequate to the safety of the drug in the proposed population will be determined during its review at the time of the NDA submission.

AstraZeneca Response:
AstraZeneca acknowledges and agrees with the FDA's response. No discussion is needed at the meeting.

Discussion during Meeting:
No discussion occurred during the meeting.

9. *Does the Agency agree that the SPRINT study, in conjunction with data from the NCI NF1 Natural History study, can support regular approval of selumetinib for the treatment of children aged 3 and above and adolescents with symptomatic and/or progressive NF1-related PNs, if the Phase II (Stratum 1) portion of SPRINT demonstrates a positive overall benefit:risk profile based on the primary endpoint and supportive data from secondary endpoints, including functional and PRO endpoints?*

FDA Response:
The data from the SPRINT study and the NCI Natural History study may support an approval of selumetinib; however, FDA does not agree that a minimum of 12 months of follow-up is adequate to fully characterize the clinical benefits and risks of selumetinib in patients with NF1 who will potentially be receiving therapy for many years. In the Phase 1 portion of the SPRINT trial, the maximum response was not reached for a median of 20 cycles (range: 5 to 42 cycles) and responses were maintained for a median of 23 cycles (range: 6 to 42 cycles). FDA recommends an additional response analysis after all patients have prolonged follow-up to better characterize the ORR and durability of response.

AstraZeneca Response:
AstraZeneca would like to discuss this topic during the meeting.

As stated by FDA, the best volumetric response for the Phase 1 was achieved after a median of approximately 20 cycles; however, most patients that had a PR (≥20% shrinkage) did so within the first year. For this reason, imaging response, PROs, and functional outcomes are assessed on the Phase 2 portion of the SPRINT study after every 4 cycles during the first year to best characterize these responses. The precycle 13 visit represents approximately one year of therapy with selumetinib, and after cycle 12, PRO and functional evaluations are performed only once per year. Though further tumor reduction may very well occur after precycle 13, based on the Phase 1 data, AstraZeneca and NCI feel the level of tumor reduction at the precycle 13 time point will demonstrate clinically meaningful benefit for patients as captured by the secondary PRO and functional endpoints.

AstraZeneca plans to also include in a NDA submission the full tables and listings as well an analysis of the tumor volume and other efficacy measures across the entire period of observation until the data cut-off of Aug 2017; we intend to formalize this proposal during a Type C, Structure and Format preNDA meeting. Based on the unvalidated summary efficacy data requested by FDA and shared by email on October 23, 2017, at the August 2017 data cut-off, volumetric responses at precycle 25 will be available for 8 (16%) patients, with a median follow-up of volumetric response of 17 cycles for all Phase 2 Stratum 1 patients.

Additionally, based on these data, there are 26 patients with at least 8 months of durable response as of the August 2017 data cut-off.

Target PN Volumetric Response	Most Recent Response as of August 31, 2017		Best Response as of August 31, 2017	
	n (%)	95% CI (%)	n (%)	95% CI (%)
No restaging evaluation	2 (4%)	(0, 14)	2 (4%)	(0, 14)
Progressive Disease (PD)	1 (2%)	(0, 11)	0 (0%)	(0, 7)
Stable Disease (SD)	17 (34%)	(21, 49)	12 (24%)	(13, 38)
Partial Response (PR + cPR + sPR)	30 (60%)	(45, 74)	36 (72%)	(58, 84)
Unconfirmed Partial Response (PR)	*3*	*(1, 17)*	*4*	*(2, 19)*
Confirmed PR (cPR)	*4*	*(2, 19)*	*6*	*(5, 24)*
Sustained PR (sPR)	*23*	*(32, 61)*	*26*	*(37, 66)*
Confirmed Response Rate (cPR + sPR)	**27 (54%)**	**(39, 68)**	**32 (64%)**	**(49, 77)**

These data were pulled from the SPRINT study database on October 13, 2017, at the request of FDA. These data are not yet clean nor fully validated.

Moreover, as presented in the briefing document, from the Phase 1 portion of SPRINT as of 31 July 2017, 17 of 24 patients remained on study, and 15 were currently on treatment. For all 24 patients in the Phase 1 portion of the study, the median number of cycles per patient was 44 (range 6 to 74 cycles). Additionally, across the entire selumetinib pediatric NF1 program, there has been no evidence to date of any new safety signals of clinical importance. As such, AstraZeneca and NCI believe that data presented with a data cut-off of August 2017 (the date when the last patient completed precycle 13 evaluations) provides sufficient evidence to evaluate the benefit:risk profile of selumetinib in patients with this rare pediatric disease.

Discussion during Meeting:
FDA stated that AstraZeneca should provide an assessment of the maturity of the data with regard to duration of response and the secondary endpoints in the meeting package for the preNDA meeting. AstraZeneca agreed to provide a response, subsequent to this meeting, as to the anticipated date that all patients with a confirmed response will have been followed for at least 12 months from the onset of response.

ADDITIONAL FDA COMMENTS

10. In general, the expectation for imaging endpoints used in a single-arm trial (to support approval) is blinded independent confirmation of the ORR and DOR results. FDA acknowledges that special expertise may be necessary to evaluate tumor size in patients with NF. With that caveat, please provide Astra Zeneca's approach for an independent radiology review of the results of the SPRINT study. For comparison, please also include an analysis of results using RECIST criteria.

AstraZeneca Response:
As acknowledged by FDA, special expertise is necessary to evaluate tumor size in patients with NF1-related PNs. AstraZeneca agrees to conduct an independent neuroradiology review of the results of the SPRINT study, and we are currently evaluating options for this review. AstraZeneca plans to present this specification to FDA, and we do not need further discussion at the meeting.

AstraZeneca would like to further discuss at the meeting the FDA recommendation to include an analysis of results using RECIST criteria.

Discussion during Meeting:
FDA clarified that the assessment of the ORR and duration of response (DoR) according to RECIST would be an exploratory analysis. AstraZeneca agreed to provide the primary patient level data for ORR and DoR by volumetric assessment and by RECIST.

11. Please clarify whether the primary endpoint for Phase 2 (ORR) is the overall confirmed partial response and complete response rate or the confirmed partial response and complete response rate at the pre-cycle 13 visit.

AstraZeneca Response:
Per protocol, the primary endpoint for the Phase 2 Stratum 1 portion of the study is the confirmed partial response and complete response rate. The primary analysis will be conducted after all patients have completed a minimum of 12 months of follow-up unless they have progressed prior to this.

Discussion during Meeting:
See discussion under Question 9.

12. Please describe the safety and efficacy data that may be available for submission to FDA from the ongoing expanded access trial under IND122851, in support of an approval for selumetinib in pediatric patients with symptomatic and/or progressive NF-1-related plexiform neurofibroma.

AstraZeneca Response:
AstraZeneca would like to discuss this topic during the meeting. Per the intermediate access protocol, no efficacy data is being collected from these patients. SAEs, ADRs, and AEs are to be collected and reported per protocol. AstraZeneca will consider strategies regarding submitting these data, and once we have full data from SPRINT, we plan to discuss any proposals regarding use of the data from the expanded access trial in support of an approval with FDA during a Type C Structure and Format meeting. At this time, we propose including narratives of SAEs, ADRs, and AEs as reported to AstraZeneca from the intermediate access protocol.

Discussion during Meeting:
AstraZeneca and NCI confirmed that patients in the SPRINT trial are not eligible for enrollment in the expanded access trial unless they were removed from the SPRINT trial for disease progression and toxicity. FDA noted that due to the limited safety data being collected in the expanded access trial, data from this trial would likely be limited to serious adverse event reports submitted in the NDA.

13. Provide an update on the status of the [redacted] (b) (4)

AstraZeneca Response:
[redacted] (b) (4)
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Discussion during Meeting:
No discussion occurred 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 marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines 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. 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 conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

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

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

ACTION ITEMS

Action Item/Description	Owner	Due Date
Anticipated date that all patients with a confirmed response will have been followed for at least 12 months from the onset of response.	AstraZeneca	TBD
Assessment of the maturity of the data regarding duration of response (FDA is seeking at least 12 months of follow-up data from the onset of response) and the secondary endpoints.	AstraZeneca	TBD
Prospective plan for analysis of functional and PRO data for FDA's review and comment	AstraZeneca	TBD

ATTACHMENTS AND HANDOUTS
AstraZeneca's presentation

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

/s/

SHARON K SICKAFUSE
11/15/2017