CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219379Orig1s000
219389Orig1s000

PRODUCT QUALITY REVIEW(S)

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Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	219379		
Applicant Name	SPRINGWORKS THERAPEUTICS INC		
Drug Product Name	GOMEKLI (mirdametinib)		
Dosage Form	Tablet, for suspension		
Proposed Strength(s)	1 mg		
NDA Classification	Type 1 - NME		
Route of Administration	Oral		
Maximum Daily Dose	8 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	GOMEKLI is a kinase inhibitor indicated for the treatment of adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN).		
Drug Product Description	Tablets for Oral Suspension 1mg: white to off-white, oval, (b) (4) grape flavored tablet, debossed with “S” on one side.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F). See USP Controlled Room Temperature. Protect from light.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Daniel Chan	Katherine Windsor

	Drug Product/ Labeling	Tefsit Bekele	Xing Wang David Claffey (labeling)
	Manufacturing	Md Abdullah Mahmud	Zhaoyang Meng
	Biopharmaceutics	Gerlie Gieser	Anitha Govada
	Microbiology	Md Abdullah Mahmud	Zhaoyang Meng
	Other (specify)	None	
	RBPM	Janell Artis	
	ATL	Xing Wang	
Consults	None		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

An expiration dating period of 30 months may be granted when stored at the proposed storage conditions.

b. Additional Comments for Action: None

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The original submission of NDA 219379 contains CMC information for (b) (4) *1 mg tablets. However, the applicant removed* (b) (4) *. The clinical pharmacology team confirmed that only keeping the 1 mg strength is acceptable based on the dosing regimen. The Applicant's request to designate Mirdametinib Tablets for Oral Suspension as a BCS Class 1 drug substance/drug product is granted. For routine QC testing of Mirdametinib Tablets, the Applicant's proposal to use disintegration testing (instead of dissolution testing) is acceptable. The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities are deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends APPROVAL of NDA219379 for GOMEKLITM (mirdametinib) tablets for oral suspension.*

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: None

Comparability Protocols (PACMP): No
Comments: None

Additional Lifecycle Comments:
None

Application Technical Lead Name and Date:

Xing Wang 12/30/2024

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	GOMEKLI™	Adequate
Established name(s)	mirdametinib	Adequate
Route(s) of administration	Capsules for oral use Tablets for oral suspension	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Capsules: 1 mg and 2 mg Tablets for oral suspension: 1 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Tablets for oral suspension Add the prescribed number of tablets to a dosing cup containing approximately 5 mL to 10 mL of drinking water. Gently swirl the water and tablets until the tablets are fully dispersed and an oral suspension is obtained. Once the tablets are dispersed, the oral suspension will appear white and cloudy. Administer the oral suspension immediately after preparation from a dosing cup or oral syringe. Discard the oral suspension if not administered within 30 minutes after preparation. After administration of the prepared suspension, add approximately 5 mL to 10 mL of drinking water to the dosing cup and gently swirl to resuspend any remaining particles. Administer the suspension to ensure the full dose is taken.	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Capsules Tablets for oral suspension	Adequate
Strength(s) in metric system	Capsules: 1 mg and 2 mg Tablets for oral suspension: 1 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	<u>Capsules</u> 1 mg: light green body and cap with "MIR 1 mg" printed on the cap in white ink. 2 mg: white body and a blue-green cap with "MIR 2 mg" printed on the cap in white ink. <u>Tablets for oral suspension</u> 1 mg: white to off-white, oval, [redacted] grape flavored tablet, debossed with "S" on one side.	Change to <u>Tablets for oral suspension</u> 1 mg: white to off-white, oval, 1 grape flavored tablet, debossed with "S" on one side.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Proprietary name: GOMEKLI Established name: Mirdametinib	Adequate
Dosage form(s) and route(s) of administration	For oral admisntration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	GOMEKLI (mirdametinib) 1 mg and 2 mg capsules (b) (4) contain 1 mg and 2 mg mirdametinib respectively in and the (b) (4): croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The gelatin capsule shell contains FD&C blue #1, gelatin (b) (4) titanium dioxide, and yellow iron oxide. The capsule is imprinted with white ink that contains butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia	Change to GOMEKLI (mirdametinib) 1 mg and 2 mg capsules contain 1 mg and 2 mg mirdametinib respectively in gelatin capsule and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The gelatin capsule shell contains FD&C blue #1, gelatin, titanium dioxide, and yellow iron oxide. The capsule is imprinted with white ink that contains butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution, and titanium dioxide.

	solution, and titanium dioxide. GOMEKLI (mirdametinib) 1 mg tablets for oral suspension contain 1 mg mirdametinib and the (b) (4) croscarmellose sodium, magnesium stearate, microcrystalline cellulose, (b) (4) grape flavor, and sucralose. The grape flavor includes corn syrup solids, modified corn starch, and triacetin.	GOMEKLI (mirdametinib) 1 mg tablets for oral suspension contain 1 mg mirdametinib and the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, grape flavor, and sucralose. The grape flavor includes corn syrup solids, modified corn starch, and triacetin.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Pharmacological/therapeutic class	kinase inhibitor	Adequate
Chemical name, structural formula, molecular weight	**Chemical name**: R)-N-(2,3-dihydroxypropoxy)-3,4-difluoro-2-((2-fluoro-4 iodophenyl) amino) benzamide **Structural formula**: $C_{16}H_{14}F_3IN_2O_4$ **Molecular weight**: 482.20 g/mol	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	Mirdametinib is a white to tan or pink solid with an aqueous solubility of 0.25 mg/mL and a pH of 7.2 in water at 25°C. (b) (4) The molecule has a pKa of 7.96.	Adequate
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Capsules Tablets for oral suspension	Adequate
Strength(s) in metric system	Capsules: 1 mg and 2 mg Tablets for oral suspension: 1mg	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 42 capsules for 1 mg and 2 mg in addition to bottles of 84 capsules for 2 mg Bottles of 42 mg and 84 tablets for tablets for oral suspension	Adequate

Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Capsules 1 mg: Light green body and cap with "MIR 1 mg" printed on the cap in white ink. 2 mg: White body and a blue green cap with "MIR 2 mg" printed on the cap in white ink. Tablets for oral suspension White to off-white, oval tablet, debossed with "S" on one side. NDC numbers are included	Make the changes shown in red to match the description provided under section 3 Tablets for oral suspension White to off-white, oval, grape flavored tablet, debossed with "S" on one side.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store capsules and tablets for oral suspension at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F). See USP Controlled Room Temperature. Protect from light.	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about (b) (4)	Not included (b) (4)	

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Spring Works Therapeutics, Inc. Stamford, CT 06902	Adequate

2.0 PATIENT LABELING

Assessment patient Labeling: Patient Labeling was edited to match the inactive ingredient list shown in section 11 of the USPI.

3.0 CARTON AND CONTAINER LABELING

12 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Container Label & Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Proprietary name: Gomeki Established name: Mirdametinib	Adequate
Dosage strength	1mg for tablets 1 mg and 2 mg for capsules	Adequate
Route of administration	Tablets for oral suspension	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	42 and 84 for 1 mg tablets 42 for 1 mg capsules 42 and 84 for 2 mg capsules	Adequate
"Rx only" displayed on the principal display	Provided	Adequate
NDC number	Provided	Adequate
Lot number and expiration date	Space provided	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Protect from light.	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Provided	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Container Label and Caron Labeling
Name of manufacturer/distributor	Manufactured for: SpringWorks Therapeutics, Inc Stamford, CT 06902	Adequate
Medication Guide (if applicable)	Provided	Adequate
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	N/A	

Assessment of Container Labels: Adequate

Overall Assessment and Recommendation:

The container labels, carton labeling and prescribing information comply with all regulatory requirements, and they are recommended for approval from a CMC perspective pending revision of what are noted in the Assessor's Comments column above.

Primary Labeling Assessor Name and Date: Tefsit Bekele December 12, 2024

Secondary Labeling Assessor Name and Date David Claffey

TEFSIT BEKELE

Digitally signed by TEFSIT BEKELE
Date: 12/23/2024 03:31:47PM
GUID: 5acb2d81000268cc7ce97540eb0a1791

David Claffey

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Date: 12/23/2024 07:23:43PM
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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA 219379
Assessment Cycle Number	1 (Original NDA; Rolling Submission)
Drug Product Name/ Strength	Mirdametinib Tablets/ [redacted] (b) (4) 1 mg
Route of Administration	Oral
Applicant Name	SpringWorks Therapeutics
Therapeutic Classification/ OND Division	Anticancer/ Division of Oncology 2 (DO2)
RLD/RS Number	(Not Applicable)
Proposed Indication	Treatment of adults and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN)
Proposed Dosage and Administration	2 mg/m^2 (maximum 4 mg) orally twice daily (with or without food) for the first 21 days of each 28-day cycle Swallow whole or disperse in about 5 mL to 10 mL water to produce a suspension for oral administration within 30 minutes of preparation. To ensure full dose is taken, rinse the dosing cup or syringe with additional 5 mL to 10 mL water, and administer the rinsing's.

Assessment Recommendation: **Adequate**

Assessment Summary:
The Applicant's request to designate Mirdametinib Tablets for Oral Suspension as a Biopharmaceutics Classification System (BCS) Class 1 (highly soluble, highly permeable) drug substance/drug product is granted.

For routine QC testing of Mirdametinib Tablets, the Applicant's proposal to use disintegration testing (instead of dissolution testing) is acceptable. [redacted] (b) (4)

[redacted] (b) (4) . The

minor CMC changes (e.g., in batch size, ingoing Active Pharmaceutical Ingredient/API manufacturer and process) that were introduced prior to commercialization did not impact the very rapid dissolution profile of Mirdametinib Tablets.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	Low		Low	BCS-1 (high solubility, high permeability)

List of Submissions Assessed:

Document(s) Assessed	Date Received
SN-2 (Pre-Submission 2 – completed Modules 3 and 4, and corresponding Module 2 summaries, and draft USPI with CMC and Nonclinical sections only 1, 2, 3, 4, 5)	5/17/2024
SN-3 (Pre-Submission 3 – pivotal clinical trial study report)	6/3/2024
SN-4 (Original NDA)	6/28/2024
SN-5 (Biopharmaceutics Early Information Request/IR Response)	7/31/2024
SN-15 (Biopharmaceutics IR Response)	9/19/2024
SN-20 (Biopharmaceutics IR Response)	10/1/2024
SN-26 (Drug Product IR Response)	10/15/2024
SN-27 (Drug Substance IR Response)	10/17/2024

Concise Description of Outstanding Issues:
None

B.1 BCS DESIGNATION

Assessment: *BCS-1 Designation Granted*

The Applicant formally requested a BCS Class-1 (high solubility, high permeability) designation for Mirdametinib Tablets (for Oral Suspension). The data/information to support the BCS-1 designation request is provided in Module 1 of the NDA (specifically Section 1.12.4).

Based on the submitted data/information, the Biopharmaceutics Assessor concludes that mirdametinib drug substance exhibits high solubility and high permeability

characteristics, and Mirdametinib Tablets for Oral Suspension are very rapidly dissolving across the physiologic pH range.

On 11/8/2024, the FDA BCS Committee voted in favor of granting BCS Class-1 status to Mirdametinib Tablets for Oral Suspension submitted in NDA 219379 (as well as Mirdametinib Capsules submitted in NDA 219389).

The Biopharmaceutics assessment of the solubility, permeability, and dissolution data submitted to support the BCS-1 designation request for the proposed drug product is provided below.

Solubility: *High*

Both the drug content of the highest strength tablet (i.e., 1 mg) and the highest therapeutic dose (4 mg) are soluble in < 250 mL media across the physiological range (pH 1.2 – 6.8; 7.5). As shown in Tables 3 and 6, Figure 1 of the BCS Class 1 Designation Request, the solubility of mirdametinib drug substance (b) (4) at 37 °C is pH independent. Per the Applicant, the buffer media pH was verified after addition of mirdametinib.

The pH-solubility profile data of the other identified/known polymorphs of mirdametinib drug substance are not available. Per the Applicant (and as confirmed by the Drug Substance Assessor), (b) (4)
(b) (4)

Permeability: *High*

Human Radiolabeled Mass Balance Study
Based on the results of the human radiolabeled mass balance clinical study (MEK-NF-101), 312 hours following a single 4 mg dose of mirdametinib (b) (4), administered as oral solution, containing approximately 80 microcuries of [^{14}C]-mirdametinib),

approximately 67.7% and 27.3% of the radioactive dose were recovered from the urine and feces, respectively, of eight healthy male subjects. Table 6 of 2.7.2 and Table 1 of MEK-NF-101 clinmet (along with evidence of gastrointestinal stability *in vitro* provided in 1.12) indicate that, to be more conservative, even if the 8.0% of the dose that was excreted in the feces as the parent drug is totally excluded, the total percentage of the mean dose eliminated from systemic circulation (%F) would still be at least 85% (also confirmed by the Clinical Pharmacology Reviewer).

Tables 3 and 4 of the MEK-NF-101 clinmet study report provide the individual subject urinary and fecal drug excretion data respectively. If excluding all parent drug found in the fecal samples, 4 of the 8 subjects would have %F <85% (minimum 79%); however, the relatively lower %F for these 4 subjects could be explained at least in part by the observation that they too had the 4 lowest total radioactive dose recovery values. This Assessor notes that in Nonclinical Study 764-05091 involving bile duct-cannulated rats, 77% (53% to 85%, n=4) of the radioactivity was recovered in bile samples over 48 hours as unchanged drug, metabolites (mainly glucuronide conjugates), and unidentified drug-related compounds, suggesting that at least part of the unchanged drug found in human fecal samples could represent absorbed drug and thus, potentially contribute to an even higher %F. It was mentioned in Report 764-04312 that in RR 764-04264, 86.6% of the radioactive dose was recovered in the bile of bile-duct cannulated rats over 144 hours. Thus, if adjusting the % Dose Eliminated in feces of each subject for the fraction of the dose (54.8%) associated only with the direct glucuronide metabolites of the parent drug in the bile of biliary cannulated rats (in Study 764-05091), all 8 human subjects in the human mass balance study would have %F of at least 85%.

This Assessor determined that it was not necessary to exclude (from the %total F) the M15 acid cleavage metabolite (the major plasma metabolite) and the M32 reductive hydrolysis metabolite fractions in the feces, based on the following lines of evidence. Based on the available *in vitro* hepatic metabolism data/information, *in vitro* gastro-intestinal stability data, and supporting *in vivo* PK data, for the purpose of high permeability assessment, it can be assumed that hepatic metabolism is mainly responsible for the formation of the parent drug cleavage and reductive hydrolysis metabolites M15 and M32, respectively.

(b) (4)

(ii) Based on *in vitro* data, it was determined that M15 (PD-0315209, the major metabolite in plasma) is produced by hepatic carboxylesterases (Report A2102065). Additionally based on literature information, it is well known that amine N-oxides [like mirdametinib] are readily reduced to the corresponding amines [like M32] by hepatic N-oxide reductases (Kitamura 1984).

(iii) Early on during development, the original IND Sponsor (Pfizer) determined that all 11 metabolites (including M15) in Figure 1 of Report 764-04904 are produced upon incubation of mirdametinib with human hepatocytes and/or liver microsomes. Also, Table 4 of Report 764-04904 shows that Metabolite M5 (designated by the NDA Sponsor/SpringWorks as Metabolite M25 in the conducted Human Mass Balance Study) was produced *in vitro* by human hepatocytes (but not by human liver microsomes). M5 was quantified in the plasma but not in the urine and feces of the 8 healthy subjects. [Note that in the *in vitro* human (and animal) hepatocyte and liver microsome studies conducted earlier by Pfizer, the chemical structures of five mirdametinib metabolites were initially "not determined", as shown in Table 4.] Figure 1 of MEK-NF-101 clinmet shows that M25 is a further metabolite of M32. If M5 (= M25, formed via metabolism of M32) is produced by human hepatocytes and microsomes (which do not contain gut microflora) *in vitro*, then it can be assumed that the liver enzymes are also responsible for parent drug metabolism to M32. It is presumed that Metabolite M32 is one the 5 metabolites whose structures were not elucidated in the Pfizer *in vitro* hepatocyte/HLM study (as shown in Table 4 of the report).

(iv) This Assessor's exploratory analysis of the clinical PK data in the pivotal clinical trial showed that there is no apparent and consistent trend showing that concomitant use of oral antibiotics/antibacterials influenced the PK parameters (e.g., AUC_{last} and Cmax) of the parent drug (mirdametinib, P0325901) and its major metabolite (P0315209, M15) in patients who participated in the pivotal clinical trial (MEK-NF-201). This observation implies that the effect of gut microflora on mirdametinib metabolism is not likely clinically significant. Refer to Assessor Table 1 below.

Assessor Table 1
Impact of Concomitant Oral Antibiotic Use on PK parameters of Parent Drug and Major Metabolite (M15); Pivotal Clinical Trial MEK-NF-201)

			PARAMCD																					
			AUCLST						CMAX						TLST						TMAX			
			AVAL						AVAL						AVAL						AVAL			
ANALYTE	AGEGR1	ConMed-PO-antibiotic	N	Mean	Std Dev	Min	Median	Max	N	Mean	Std Dev	Min	Median	Max	N	Mean	Std Dev	Min	Median	Max	N	Mean	Std Dev	Min	Median	Max
P0325901	>=18	No	13.0	461.5	165.6	159.8	493.9	750.1	13.0	219.8	99.3	65.5	236.0	360.0	13.0	4.0	0.1	3.8	4.0	4.3	13.0	1.5	1.1	0.0	1.1	4.2
		Yes	41.0	467.5	180.2	178.2	471.1	939.8	41.0	206.5	94.2	72.2	207.0	487.0	41.0	4.0	0.1	3.8	4.0	4.1	41.0	1.5	0.9	0.4	1.1	4.0
	9 to 17	No	16.0	422.0	143.3	145.9	422.7	633.3	16.0	194.5	97.8	49.0	191.0	398.0	16.0	3.9	0.1	3.8	4.0	4.1	16.0	1.5	1.3	0.0	1.0	4.0
		Yes	14.0	496.0	205.9	134.1	561.1	784.9	14.0	207.3	120.2	37.2	193.5	467.0	14.0	4.0	0.1	3.9	4.0	4.2	14.0	1.6	0.8	0.5	1.5	3.0
	2 to <9	No	8.0	555.3	268.6	211.5	505.9	1004.5	8.0	261.5	162.8	85.8	239.0	573.0	8.0	4.0	0.1	3.9	4.0	4.1	8.0	1.4	1.0	0.5	1.0	3.0
		Yes	15.0	551.8	164.0	352.3	512.3	911.6	15.0	237.7	93.1	122.0	183.0	410.0	15.0	4.0	0.1	3.9	4.0	4.1	15.0	0.9	0.4	0.5	1.0	2.0
P0315209	>=18	No	13.0	286.9	236.0	10.3	223.0	909.6	13.0	80.3	67.5	3.1	64.4	267.0	13.0	4.0	0.1	3.8	4.0	4.3	13.0	2.5	1.1	0.8	2.0	4.2
		Yes	41.0	281.5	156.1	46.9	252.0	600.7	41.0	79.1	42.8	13.5	70.4	162.0	41.0	4.0	0.1	3.8	4.0	4.1	41.0	2.3	1.1	0.0	2.0	4.0
	9 to 17	No	16.0	249.5	100.6	31.9	254.0	439.3	16.0	71.8	27.9	9.7	76.8	120.0	16.0	3.9	0.1	3.8	4.0	4.1	16.0	1.6	1.4	0.0	1.0	4.1
		Yes	14.0	247.9	132.3	12.5	249.8	466.4	14.0	68.7	36.8	3.6	68.8	131.0	14.0	4.0	0.1	3.9	4.0	4.2	14.0	2.5	1.2	0.0	2.9	4.2
	2 to <9	No	8.0	197.4	135.5	66.3	150.7	395.2	8.0	55.4	36.7	18.1	46.7	105.0	8.0	4.0	0.1	3.9	4.0	4.1	8.0	2.5	1.1	1.1	2.0	4.1
		Yes	15.0	192.9	115.0	64.4	137.6	407.5	15.0	54.4	33.4	17.5	38.0	114.0	15.0	4.0	0.1	3.9	4.0	4.1	15.0	2.1	1.2	0.0	2.0	4.1

AGEGR1 (Age subgroup); ConMed-PO-antibiotic (Concomitant use of Oral Antibacterials); AUCLST(AUC_{0-t}); TLST (last timepoint); AVAL (Value)

Moreover, because it appears that at least 4 of the 12 oxidative/glucuronidated metabolites identified by *in vitro* human liver microsome and hepatocyte studies (Report 764-04904) were not quantified (or accounted for) in the urine and fecal

samples of Study MEK-NF-101, there is a possibility that the %F obtained from the human mass balance study is an underestimate (i.e., F >> 85%).

Therefore, based mainly on *in vivo* human PK data, it can be concluded that the fraction of the mirdametinib dose that reaches systemic circulation (%F) is high (i.e., at least 85%).

This Assessor determines that the findings of the human mass balance study, using the [redacted] (b) (4) oral solution, can be extrapolated to the proposed to-be-marketed dosage form, i.e., oral tablets for suspension (as well as the oral capsule), considering the following observations: (***i***) the comparable dose- and bodyweight- normalized mean mirdametinib PK profile data of the PIB oral solution and the oral capsules [redacted] (b) (4) 2 mg, 1 mg) in healthy adult subjects/patients, (***ii***) the comparable mean mirdametinib PK parameter data of the oral solution and the oral capsules (1 mg, 2 mg) after a single 4 mg dose in healthy adult subjects/patients, and (***iii***) the comparable mean AUC_{0-4} and Cmax data of the oral capsules (taken whole) and the oral tablets (given as suspension) in age-matched pediatric patients in the pivotal clinical trial (SN-7 IR Response).

In Vitro Caco-2 Permeability Study

In Caco-2 Study 23SPRWP2, the apical-to-basolateral apparent permeability coefficients ($P_{app, A\rightarrow B}$) of mirdametinib at 0.332 μM and 33.2 μM dosing concentrations tested (representing 1% and 100%, respectively, based on maximum therapeutic dose of 4 mg in 250 mL) were 13.8 x 10^{-6} cm/s and 13.2 x 10^{-6} cm/s, respectively (refer to Table 6 of the study report). It is noted that these P_{app} values at both concentrations are greater than (two-fold higher than) the $P_{app, A\rightarrow B}$ of minoxidil 10 μM (the co-dosed high permeability internal standard, ~3.6 x 10^{-6} cm/s). It is also noted from the results of this uni-directional study that the Caco-2 $P_{app, A\rightarrow B}$ value at 0.332 μM dosing concentration is almost the same as that measured for 33.2 μM dosing concentration. This apparent drug concentration-independent *in vitro* drug permeation across the Caco-2 epithelium suggests that (even at the lowest initial drug concentration) passive diffusion is the predominant drug transport mechanism for mirdametinib.

Based on the results of the 1st bi-directional Caco-2 study (without co-dosed reference compounds), at 0.332 μM (the lowest drug dosing concentration evaluated in the Caco-2 study; representing the plasma C_{max} after a single 4 mg dose of the PIB oral solution), the efflux ratio is a little over 2.0 (Table 7), which suggests that the drug may be a substrate of an apical drug efflux transporter such as P-glycoprotein/P-gp at low (i.e., systemic) drug concentrations. [The proposed labeling states that mirdametinib is a substrate of drug efflux transporters (i.e., BCRP and P-glycoprotein/P-gp).] Based on the results of a 2nd bidirectional Caco-2 study (Study 764-04274, Table 1) at higher initial drug concentration, i.e., 20 μM (representing ~60% of 4 mg/250 mL mirdametinib in the gut), the efflux ratio is ~1.0, indicating that at this higher drug concentration the active drug (efflux) transporter's activity is saturated (and thus, net effect of drug efflux would be minimal). In the 3rd

bidirectional Caco-2 study (24SPRWP2) submitted recently (in SN-20); the efflux ratios at mirdametinib dosing concentrations of 3.32 μM and 33.2 μM were 1.96 and 0.819, respectively. There are three lines of clinical evidence for the minimal to no effect of apical drug efflux transporters (e.g., P-gp) on mirdametinib *in vivo* absorption/bioavailability:

(1) The results of the *in vivo* human radiolabeled mass balance study indicate a high fraction absorbed (Fa) for mirdametinib.
(2) Based on the Applicant's Population PK Analysis, concomitant administration of P-gp inhibitors did not impact mirdametinib exposures in humans.
(3) In a dose-ranging PK study (Study A4581001), the exposures to the drug were observed to be dose proportional and mirdametinib PK was observed to be generally linear over the 1 mg to 20 mg dose range (which also further supports passive diffusion as the predominant transport mechanism for mirdametinib).

Note that in SN-4, the Applicant clarified that the Caco-2 permeability studies (as well as method validation) were conducted by (b) (4)

(b) (4)

(b) (4)

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(b) (4)

The aqueous solubility of mirdametinib is 0.25 mg/mL at 25 °C in water. (b) (4) Per the proposed labeling, a dosing *suspension* may be prepared by dispersing the prescribed number of tablets in 5 mL to 10 mL water in a dosing cup.

This Assessor recommends removal of the following statement from the proposed labeling: (b) (4) , this Assessor believes that the following drug substance solubility information is sufficient and is more relevant to the preparation instructions for the dispersible tablets prior to oral administration: “Mirdametinib is a white to tan or pink solid with an aqueous solubility of 0.25 mg/mL and a pH of 7.2 in water at 25°C.”

(b) (4)

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(b) (4)

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Proposal to Use Disintegration in Lieu of Dissolution for Routine QC Testing of Tablets - *Acceptable*

The Applicant's proposal to use disintegration instead of dissolution for routine QC testing of the proposed Mirdametinib Tablets at batch release and during shelf-life (in accordance with the ICH Q6A Guidelines and Decision Tree #7) is acceptable based on the following considerations/observations:

1. The proposed drug product is designed for immediate drug release.
2. Prior to oral administration, the proposed drug product is dispersed in 5 mL to 10 mL water to form an oral suspension.
3. As indicated in Review Section B.1 above, the proposed drug product contains an active ingredient that is highly soluble at 37 °C across the physiologic pH range (b) (4). In addition, the active pharmaceutical ingredient exhibits the characteristics of a high permeability drug substance. Note that on 11/8/2024, the FDA BCS Committee voted in favor of granting the BCS Class 1 designation request for Mirdametinib Tablets for Oral Suspension.

(b) (4)

(b) (4)

7. The Drug Product Assessor recommended tightening of the disintegration acceptance criterion to (b) (4) In SN-26, the Applicant revised the finished product QC specifications to reflect agreement with FDA's recommendation. For this Biopharmaceutics Assessor's input regarding the disintegration acceptance criterion for the dispersible tablets that was conveyed to the OPQ Review Team, refer to the section below on "Dissolution and Disintegration on Stability".
8. Additionally, the Applicant agreed with the Drug Substance Assessor's recommendation to include (b) (4) in the drug substance QC specifications.

(b) (4)

(b) (4)

(b) (4)

(b) (4) Disintegration on Stability

(b) (4)

(b) (4) as well as to the proposed disintegration time of (b) (4) with no apparent trends. Refer to Table 22 to Table 31 of the DMDR, or 3.2.P.8.3 Stability Data.

Note that per the Applicant, the disintegration on stability data of the registration batches of Mirdametinib Tablets ranged from (b) (4)' (as shown in Table 32 of the DMDR). Per the Applicant, based on historical data of the clinical and registration batches, the proposed disintegration tolerance limit for the tablets is ' (b) (4) . As stated above, the Applicant tightened the dispersible tablet's disintegration time to (b) (4) based on FDA recommendation.

This Assessor agrees with the recommendation to tighten the proposed disintegration tolerance limit, based on the disintegration data of the pivotal clinical trial lots of Mirdametinib Tablets at batch release (b) (4) and during long-term/intermediate/accelerated stability testing (b) (4)

(b) (4)

Per the Drug Product Assessor, the proposed expiration dating period of 30 months for Mirdametinib dispersible tablets stored at 15 – 25 °C in the commercial packaging configurations is acceptable.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: *Not Applicable*

(b) (4)

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: *Not Applicable*

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

Compared to the Mirdametinib Tablet lots evaluated in the pivotal Phase 2b clinical study (MEK-NF-201, ReNeu) and in primary registration/stability studies, the proposed to-be-marketed Mirdametinib Tablets have the same formulation composition and manufacturing process, were manufactured at comparable scale by the same drug product manufacture (b) (4) using the drug substance from the same API manufacturer (b) (4) and met the same commercial QC specifications, (b) (4) . Additionally, the appearance of the proposed to-be-marketed Mirdametinib Tablets (1 mg) provided in the final proposed labeling in SN-4, i.e., “White to off-white, oval tablet, debossed with “S” on one side”, is the same as described for the registration and pivotal clinical trial lot (CFTZZ) in 3.2.P.5.4 and 3.2.P.8.3.The primary packaging of the registration batches is also the same as proposed for marketing, i.e., HDPE bottles with (b) (4) closure: (b) (4) 1 mg, 30 cc with 42 or 84 tabs).

(b) (4)

- Also, the Drug Substance Assessor confirmed that the proposed commercial API (b) (4) process is essentially the same as that used in late-stage (including the pivotal) clinical trials, the drug substance and drug product registration stability studies.

ASSESSOR NOTE (Bridging Data Between Tablets and Capsules):
According to Table 4 of 2.7.1, the only clinical study that used both Mirdametinib Tablets (0.5 mg and 1 mg) and Mirdametinib Capsules (1 mg and 2 mg) as anticancer monotherapy in the intended patient population is the pivotal Phase 2b clinical trial (Study MEK NF-201). Another Phase 2 clinical trial (Study NF-106) also used the 1 mg capsules (as monotherapy in the intended population).

In the Type C CMC WRO Meeting Minutes dated 4/9/2020, the FDA indicated no objection to the introduction of the pediatric formulation (dispersible tablets) to the ongoing pivotal clinical Study MEK-NF-201, which has been dosing patients >12 years old with the Mirdametinib Capsules.

Previously in SN-107 of the IND (139883), the Applicant reported that pediatric patients in the pivotal Phase 2 clinical trial (MEK-NF-201) exhibited preliminary PK parameters (i.e., T_{max}, C_{max}, AUC_{last}) that were similar between the capsule (1 mg and 2 mg) and tablet (b) (4) 1 mg) formulations. In SN-3 of the NDA (219379), the Applicant provided clinical PK data for the final to-be-marketed dosage forms/formulations of mirdametinib from pivotal clinical Study MEK-NF-201, as recommended. Per the Applicant, in the pediatric cohort, mirdametinib PK parameters and overall exposures were generally comparable between the capsules and the tablets; refer to the tables and figures in Section 11.2.5.1.3 of the MEK-NF-201 CSR. Additionally, based on the Applicant's Population PK analyses, there was no statistically significant difference in mirdametinib exposures observed among participants who received the capsule and the tablet formulations. Of note, the Clinical Pharmacology Assessor confirmed that in a subset of pediatric patients (in the overlapping age range of '5 to 14 years old') who received either the oral capsule or the tablet for oral suspension in the pivotal clinical trial (MEK-NF-201), the mean mirdametinib Cmax and AUC were comparable between dosage form groups.

- Thus, because clinical PK data are already available for both the proposed commercial tablets (for suspension) and capsules, this Biopharmaceutics Assessor determined that a request to waive *in vivo* BE testing of the tablets versus capsules is not needed. Also note that in the Biopharmaceutics Information Request dated 3/27/2024 under the IND, the Sponsor was informed that per the ICH M9 Guidance, products with different dosage forms and strengths are not eligible for a BCS-based biowaiver.

Table 2 of 2.3.P (or Table 34 of 3.2.P.2.3/NDA 21379 and Table 32 of 3.2.P.2.3/NDA 217389) lists the batch numbers and other CMC information of the mirdametinib dosage forms and formulations used in clinical studies.

(b) (4)

B. 13 BIOWAIVER REQUEST

Assessment: *Not Needed*

(b) (4) 1 mg strengths of the proposed to-be-marketed Mirdametinib Tablets were used in the pivotal clinical trial. Thus, a biowaiver request for a proposed commercial strength not used in clinical studies is not needed.

(b) (4)

(b) (4)

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: *Not Applicable*

Post-Approval Commitments

Assessment: *None*

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date: Gerlie Gieser, Ph.D. (12/2/2024)

Secondary Assessor Name and Date: Anitha Govada, Ph.D. (12/11/2024)

Gerlie Gieser

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Anitha Palamakula Govada

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Xing Wang

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/s/

XING WANG
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Template Revision: 03

Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	219389		
Applicant Name	SPRINGWORKS THERAPEUTICS INC		
Drug Product Name	GOMEKLI (mirdametinib)		
Dosage Form	Capsule		
Proposed Strength(s)	1 mg and 2 mg		
NDA Classification	Type 1 - NME		
Route of Administration	Oral		
Maximum Daily Dose	8 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	GOMEKLI is a kinase inhibitor indicated for the treatment of adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN).		
Drug Product Description	Capsules: • 1 mg: light green body and cap with “MIR 1 mg” printed on the cap in white ink. • 2 mg: white body and a blue-green cap with “MIR 2 mg” printed on the cap in white ink.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F). See USP Controlled Room Temperature. Protect from light.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Daniel Chan	Katherine Windsor

	Drug Product/ Labeling	Tefsit Bekele	Xing Wang David Claffey (labeling)
	Manufacturing	Md Abdullah Mahmud	Zhaoyang Meng
	Biopharmaceutics	Gerlie Gieser	Anitha Govada
	Microbiology	Md Abdullah Mahmud	Zhaoyang Meng
	Other (specify)	None	
	RBPM	Janell Artis	
	ATL	Xing Wang	
Consults	None		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

An expiration dating period of 36 months may be granted when stored at the proposed storage conditions.

b. Additional Comments for Action: None

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The applicant submitted two NDAs for mirdametinib tablet (NDA 219379) and mirdametinib capsule (NDA 218389) formulation concurrently. NDA 219389 contains relevant data to support the capsule formulation and cross-references all other modules in mirdametinib tablet NDA 219379 for supporting data. The Applicant's request to designate Mirdametinib Capsules as a BCS) Class 1 drug substance/drug product is granted. The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities are deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends APPROVAL of NDA219389 for GOMEKLITM (mirdametinib) capsules, for oral use.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. **Life-Cycle Considerations**

Established Conditions per ICH Q12: No
Comments: None

Comparability Protocols (PACMP): No
Comments: None

Additional Lifecycle Comments:
None

Application Technical Lead Name and Date:

Xing Wang 12/30/2024

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	GOMEKLI™	Adequate
Established name(s)	mirdametinib	Adequate
Route(s) of administration	Capsules for oral use Tablets for oral suspension	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Capsules: 1 mg and 2 mg Tablets for oral suspension: 1 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Tablets for oral suspension Add the prescribed number of tablets to a dosing cup containing approximately 5 mL to 10 mL of drinking water. Gently swirl the water and tablets until the tablets are fully dispersed and an oral suspension is obtained. Once the tablets are dispersed, the oral suspension will appear white and cloudy. Administer the oral suspension immediately after preparation from a dosing cup or oral syringe. Discard the oral suspension if not administered within 30 minutes after preparation. After administration of the prepared suspension, add approximately 5 mL to 10 mL of drinking water to the dosing cup and gently swirl to resuspend any remaining particles. Administer the suspension to ensure the full dose is taken.	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Capsules Tablets for oral suspension	Adequate
Strength(s) in metric system	Capsules: 1 mg and 2 mg Tablets for oral suspension: 1 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	<u>Capsules</u> 1 mg: light green body and cap with "MIR 1 mg" printed on the cap in white ink. 2 mg: white body and a blue-green cap with "MIR 2 mg" printed on the cap in white ink. <u>Tablets for oral suspension</u> 1 mg: white to off-white, oval, [redacted] grape flavored tablet, debossed with "S" on one side.	Change to <u>Tablets for oral suspension</u> 1 mg: white to off-white, oval, 1 grape flavored tablet, debossed with "S" on one side.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Proprietary name: GOMEKLI Established name: Mirdametinib	Adequate
Dosage form(s) and route(s) of administration	For oral admisntration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	GOMEKLI (mirdametinib) 1 mg and 2 mg capsules (b) (4) contain 1 mg and 2 mg mirdametinib respectively in and the (b) (4) croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The gelatin capsule shell contains FD&C blue #1, gelatin (b) (4) titanium dioxide, and yellow iron oxide. The capsule is imprinted with white ink that contains butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia	Change to GOMEKLI (mirdametinib) 1 mg and 2 mg capsules contain 1 mg and 2 mg mirdametinib respectively in gelatin capsule and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The gelatin capsule shell contains FD&C blue #1, gelatin, titanium dioxide, and yellow iron oxide. The capsule is imprinted with white ink that contains butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution, and titanium dioxide.

	solution, and titanium dioxide. GOMEKLI (mirdametinib) 1 mg tablets for oral suspension contain 1 mg mirdametinib and the [redacted] croscarmellose sodium, magnesium stearate, microcrystalline cellulose, [redacted] grape flavor, and sucralose. The grape flavor includes corn syrup solids, modified corn starch, and triacetin.	GOMEKLI (mirdametinib) 1 mg tablets for oral suspension contain 1 mg mirdametinib and the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, grape flavor, and sucralose. The grape flavor includes corn syrup solids, modified corn starch, and triacetin.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Pharmacological/therapeutic class	kinase inhibitor	Adequate
Chemical name, structural formula, molecular weight	**Chemical name**: R)-N-(2,3-dihydroxypropoxy)-3,4-difluoro-2-((2-fluoro-4 iodophenyl) amino) benzamide **Structural formula**: $C_{16}H_{14}F_3IN_2O_4$ **Molecular weight**: 482.20 g/mol	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	Mirdametinib is a white to tan or pink solid with an aqueous solubility of 0.25 mg/mL and a pH of 7.2 in water at 25°C. (b) (4) The molecule has a pKa of 7.96.	Adequate
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Capsules Tablets for oral suspension	Adequate
Strength(s) in metric system	Capsules: 1 mg and 2 mg Tablets for oral suspension: 1mg	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 42 capsules for 1 mg and 2 mg in addition to bottles of 84 capsules for 2 mg Bottles of 42 mg and 84 tablets for tablets for oral suspension	Adequate

Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Capsules 1 mg: Light green body and cap with "MIR 1 mg" printed on the cap in white ink. 2 mg: White body and a blue green cap with "MIR 2 mg" printed on the cap in white ink. Tablets for oral suspension White to off-white, oval tablet, debossed with "S" on one side. NDC numbers are included	Make the changes shown in red to match the description provided under section 3 Tablets for oral suspension White to off-white, oval, grape flavored tablet, debossed with "S" on one side.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store capsules and tablets for oral suspension at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F). See USP Controlled Room Temperature. Protect from light.	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about (b) (4)	Not included (b) (4)	

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Spring Works Therapeutics, Inc. Stamford, CT 06902	Adequate

2.0 PATIENT LABELING

Assessment patient Labeling: Patient Labeling was edited to match the inactive ingredient list shown in section 11 of the USPI.

3.0 CARTON AND CONTAINER LABELING

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Item	Information Provided in the NDA	Assessor's Comments about Container Label & Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Proprietary name: Gomeki Established name: Mirdametinib	Adequate
Dosage strength	1mg for tablets 1 mg and 2 mg for capsules	Adequate
Route of administration	Tablets for oral suspension	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	42 and 84 for 1 mg tablets 42 for 1 mg capsules 42 and 84 for 2 mg capsules	Adequate
"Rx only" displayed on the principal display	Provided	Adequate
NDC number	Provided	Adequate
Lot number and expiration date	Space provided	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Protect from light.	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Provided	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Container Label and Caron Labeling
Name of manufacturer/distributor	Manufactured for: SpringWorks Therapeutics, Inc Stamford, CT 06902	Adequate
Medication Guide (if applicable)	Provided	Adequate
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	N/A	

Assessment of Container Labels: Adequate

Overall Assessment and Recommendation:

The container labels, carton labeling and prescribing information comply with all regulatory requirements, and they are recommended for approval from a CMC perspective pending revision of what are noted in the Assessor's Comments column above.

Primary Labeling Assessor Name and Date: Tefsit Bekele December 12, 2024

Secondary Labeling Assessor Name and Date David Claffey

TEFSIT BEKELE

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Date: 12/23/2024 03:33:21PM
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David Claffey

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Date: 12/23/2024 07:23:32PM
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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA 219389
Assessment Cycle Number	1 (Original NDA; Rolling Submission)
Drug Product Name/ Strength	Mirdametinib Capsules/ 1 mg and 2 mg
Route of Administration	Oral
Applicant Name	SpringWorks Therapeutics
Therapeutic Classification/ OND Division	Anticancer/ Division of Oncology 2 (DO2)
RLD/RS Number	(Not Applicable)
Proposed Indication	Treatment of adults and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN)
Proposed Dosage and Administration	2 mg/m^2 (maximum 4 mg) orally twice daily (with or without food) for the first 21 days of each 28-day cycle Swallow whole.

Assessment Recommendation: **Adequate**

Assessment Summary:
The Applicant's request to designate Mirdametinib Capsules as a Biopharmaceutics Classification System (BCS) Class 1 (highly soluble, highly permeable) drug substance/drug product is granted.

The proposed dissolution method parameters [USP Apparatus 1 (basket) at 75 rpm; 500 mL of 0.1N HCl] and acceptance criteria (Q = (b) (4) at 30 min) are acceptable for routine QC (and comparability) testing of Mirdametinib Capsules.

Both strengths (1 mg and 2 mg) of the proposed commercial Mirdametinib Capsules were evaluated in clinical PK, efficacy, and safety studies (as well as in stability studies). Thus, a biowaiver was not requested nor required. The minor CMC changes (e.g., in capsule shell appearance, capsule batch size, ingoing Active Pharmaceutical Ingredient/API manufacturer and process) that were introduced prior to commercialization did not impact the rapid to very rapid dissolution profile of Mirdametinib Capsules.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle # 1	Comments
Dissolution	Low		Low	BCS-1 (high solubility, high permeability)

List of Submissions Assessed:

Document(s) Assessed	Date Received
SN-21(Clinical Pharmacology Information Request/IR Response)	10/1/2024
SN-1 (Pre-Submission 1)	5/17/2024
SN-2 (Original NDA)	6/28/2024
SN-4 (Biopharmaceutics Early IR Response)	7/31/2024
SN-7 (Biopharmaceutics IR Response)	9/19/2024
SN-11 (Drug Product IR Response – including dissolution analytical method validation)	10/7/2024
SN-14 (Response to Drug Product IR – capsule shelf-life)	10/21/2024

Concise Description of Outstanding Issues:
None

B.1 BCS DESIGNATION

Assessment: *BCS-1 Designation Granted*

The Applicant formally requested a BCS Class-1 (high solubility, high permeability) designation for Mirdametinib Capsules. The data/information to support the BCS-1 designation request is provided in 1.12.4 (via cross-reference to NDA 219379).

Based on the submitted data/information, the Biopharmaceutics Assessor concludes that mirdametinib drug substance exhibits high solubility and high permeability characteristics, and Mirdametinib Oral Capsules are rapidly dissolving across the physiologic pH range.

On 11/8/2024, the FDA BCS Committee voted in favor of granting BCS Class-1 status to Mirdametinib Capsules submitted in NDA 219379 (as well as Mirdametinib Tablets for Oral Suspension submitted in NDA 219389).

The Biopharmaceutics assessment of the solubility, permeability, and dissolution data submitted to support the BCS-1 designation request is provided below.

Solubility: *High*
Both the drug content of the highest strength tablet (i.e., 1 mg) and the highest therapeutic dose (4 mg) are soluble in < 250 mL media across the physiological range (pH 1.2 – 6.8; 7.5). As shown in Tables 3 and 6, Figure 1 of the BCS Class 1 Designation Request, the solubility of mirdametinib drug substance (b) (4) at 37 °C is pH independent. Per the Applicant, the buffer media pH was verified after addition of mirdametinib.

The pH-solubility profile data of the other identified/known polymorphs of mirdametinib drug substance are not available. Per the Applicant (and as confirmed by the Drug Substance Assessor), (b) (4) is the most thermodynamically stable API polymorphic form of mirdametinib drug substance. (b) (4)

(b) (4)

Permeability: *High*

Human Radiolabeled Mass Balance Study
Based on the results of the human radiolabeled mass balance clinical study (MEK-NF-101), 312 hours following a single 4 mg dose of mirdametinib (b) (4), administered as oral solution, containing approximately 80 microcuries of [^{14}C]-mirdametinib), approximately 67.7% and 27.3% of the radioactive dose were recovered from the urine and feces, respectively, of eight healthy male subjects. Table 6 of 2.7.2 and Table 1 of MEK-NF-101 clinmet (along with evidence of gastrointestinal stability *in vitro* provided in 1.12) indicate that, to be more conservative, even if the 8.0% of the dose that was excreted in the feces as the parent drug is totally excluded, the total percentage of the mean dose eliminated from systemic circulation (%F) would still be at least 85% (also confirmed by the Clinical Pharmacology Reviewer).

Tables 3 and 4 of the MEK-NF-101 clinmet study report provide the individual subject urinary and fecal drug excretion data respectively. If excluding all parent drug found in the fecal samples, 4 of the 8 subjects would have %F <85% (minimum 79%); however, the relatively lower %F for these 4 subjects could be explained at least in part by the observation that they too had the 4 lowest total radioactive dose recovery values. This Assessor notes that in Nonclinical Study 764-05091 involving bile duct-cannulated rats, 77% (53% to 85%, n=4) of the radioactivity was recovered in bile samples over 48 hours as unchanged drug, metabolites (mainly glucuronide conjugates), and unidentified drug-related compounds, suggesting that at least part of the unchanged drug found in human fecal samples could represent absorbed drug and thus, potentially contribute to an even higher %F. It was mentioned in Report 764-04312 that in RR 764-04264, 86.6% of the radioactive dose was recovered in the bile of bile-duct cannulated rats over 144 hours. Thus, if adjusting the % Dose Eliminated in feces of each subject for the fraction of the dose (54.8%) associated only with the direct glucuronide metabolites of the parent drug in the bile of biliary cannulated rats (in Study 764-05091), all 8 human subjects in the human mass balance study would have %F of at least 85%.

This Assessor determined that it was not necessary to exclude (from the %total F) the M15 acid cleavage metabolite (the major plasma metabolite) and the M32 reductive hydrolysis metabolite fractions in the feces, based on the following lines of evidence. Based on the available *in vitro* hepatic metabolism data/information, *in vitro* gastro-intestinal stability data, and supporting *in vivo* PK data, for the purpose of high permeability assessment, it can be assumed that hepatic metabolism is mainly responsible for the formation of the parent drug cleavage and reductive hydrolysis metabolites M15 and M32, respectively.

(i) (b) (4) .

(ii) Based on *in vitro* data, it was determined that M15 (PD-0315209, the major metabolite in plasma) is produced by hepatic carboxylesterases (Report A2102065). Additionally based on literature information, it is well known that amine N-oxides [like mirdametinib] are readily reduced to the corresponding amines [like M32] by hepatic N-oxide reductases (Kitamura 1984).

(iii) Early on during development, the original IND Sponsor (Pfizer) determined that all 11 metabolites (including M15) in Figure 1 of Report 764-04904 are produced upon incubation of mirdametinib with human hepatocytes and/or liver microsomes. Also, Table 4 of Report 764-04904 shows that Metabolite M5 (designated by the NDA Sponsor/SpringWorks as Metabolite M25 in the conducted Human Mass Balance Study) was produced *in vitro* by human hepatocytes (but not by human liver microsomes). M5 was quantified in the

plasma but not in the urine and feces of the 8 healthy subjects. [Note that in the *in vitro* human (and animal) hepatocyte and liver microsome studies conducted earlier by Pfizer, the chemical structures of five mirdametinib metabolites were initially "not determined", as shown in Table 4.] Figure 1 of MEK-NF-101 clinmet shows that M25 is a further metabolite of M32. If M5 (= M25, formed via metabolism of M32) is produced by human hepatocytes and microsomes (which do not contain gut microflora) *in vitro*, then it can be assumed that the liver enzymes are also responsible for parent drug metabolism to M32. It is presumed that Metabolite M32 is one the 5 metabolites whose structures were not elucidated in the Pfizer *in vitro* hepatocyte/HLM study (as shown in Table 4 of the report).

(iv) This Assessor's exploratory analysis of the clinical PK data in the pivotal clinical trial showed that there is no apparent and consistent trend showing that concomitant use of oral antibiotics/antibacterials influenced the PK parameters (e.g., AUC_{last} and Cmax) of the parent drug (mirdametinib, P0325901) and its major metabolite (P0315209, M15) in patients who participated in the pivotal clinical trial (MEK-NF-201). This observation implies that the effect of gut microflora on mirdametinib metabolism is not likely clinically significant. Refer to Assessor Table 1 below.

Assessor Table 1
Impact of Concomitant Oral Antibiotic Use on PK parameters of Parent Drug and Major Metabolite (M15); Pivotal Clinical Trial MEK-NF-201)

			PARAMCD																					
			AUCLST						CMAX						TLST						TMAX					
			AVAL						AVAL						AVAL						AVAL					
ANALYTE	AGEGR1	ConMed-PO-antibiotic	N	Mean	Std Dev	Min	Median	Max	N	Mean	Std Dev	Min	Median	Max	N	Mean	Std Dev	Min	Median	Max	N	Mean	Std Dev	Min	Median	Max
P0325901	>=18	No	13.0	461.5	165.6	159.8	493.9	750.1	13.0	219.8	99.3	65.5	236.0	360.0	13.0	4.0	0.1	3.8	4.0	4.3	13.0	1.5	1.1	0.0	1.1	4.2
		Yes	41.0	467.5	180.2	178.2	471.1	939.8	41.0	206.5	94.2	72.2	207.0	487.0	41.0	4.0	0.1	3.8	4.0	4.1	41.0	1.5	0.9	0.4	1.1	4.0
	9 to 17	No	16.0	422.0	143.3	145.9	422.7	633.3	16.0	194.5	97.8	49.0	191.0	398.0	16.0	3.9	0.1	3.8	4.0	4.1	16.0	1.5	1.3	0.0	1.0	4.0
		Yes	14.0	496.0	205.9	134.1	561.1	784.9	14.0	207.3	120.2	37.2	193.5	467.0	14.0	4.0	0.1	3.9	4.0	4.2	14.0	1.6	0.8	0.5	1.5	3.0
	2 to <9	No	8.0	555.3	268.6	211.5	505.9	1004.5	8.0	261.5	162.8	85.8	239.0	573.0	8.0	4.0	0.1	3.9	4.0	4.1	8.0	1.4	1.0	0.5	1.0	3.0
		Yes	15.0	551.8	164.0	352.3	512.3	911.6	15.0	237.7	93.1	122.0	183.0	410.0	15.0	4.0	0.1	3.9	4.0	4.1	15.0	0.9	0.4	0.5	1.0	2.0
P0315209	>=18	No	13.0	286.9	236.0	10.3	223.0	909.6	13.0	80.3	67.5	3.1	64.4	267.0	13.0	4.0	0.1	3.8	4.0	4.3	13.0	2.5	1.1	0.8	2.0	4.2
		Yes	41.0	281.5	156.1	46.9	252.0	600.7	41.0	79.1	42.8	13.5	70.4	162.0	41.0	4.0	0.1	3.8	4.0	4.1	41.0	2.3	1.1	0.0	2.0	4.0
	9 to 17	No	16.0	249.5	100.6	31.9	254.0	439.3	16.0	71.8	27.9	9.7	76.8	120.0	16.0	3.9	0.1	3.8	4.0	4.1	16.0	1.6	1.4	0.0	1.0	4.1
		Yes	14.0	247.9	132.3	12.5	249.8	466.4	14.0	68.7	36.8	3.6	68.8	131.0	14.0	4.0	0.1	3.9	4.0	4.2	14.0	2.5	1.2	0.0	2.9	4.2
	2 to <9	No	8.0	197.4	135.5	66.3	150.7	395.2	8.0	55.4	36.7	18.1	46.7	105.0	8.0	4.0	0.1	3.9	4.0	4.1	8.0	2.5	1.1	1.1	2.0	4.1
		Yes	15.0	192.9	115.0	64.4	137.6	407.5	15.0	54.4	33.4	17.5	38.0	114.0	15.0	4.0	0.1	3.9	4.0	4.1	15.0	2.1	1.2	0.0	2.0	4.1

AGEGR1 (Age subgroup); ConMed-PO-antibiotic (Concomitant use of Oral Antibacterials); AUCLST(AUC_{0-t}); TLST (last timepoint); AVAL (Value)

Moreover, because it appears that at least 4 of the 12 oxidative/glucuronidated metabolites identified by *in vitro* human liver microsome and hepatocyte studies (Report 764-04904) were not quantified (or accounted for) in the urine and fecal samples of Study MEK-NF-101, there is a possibility that the %F obtained from the human mass balance study is an underestimate (i.e., F >> 85%).

Therefore, based mainly on *in vivo* human PK data, it can be concluded that the fraction of the mirdametinib dose that reaches systemic circulation (%F) is high (i.e., at least 85%).

This Assessor determines that the findings of the human mass balance study, using the [redacted] (b) (4) oral solution, can be extrapolated to the proposed to-be-marketed dosage forms, i.e., oral capsule (as well as the oral tablets for suspension), considering the following observations: (***i***) the comparable dose- and bodyweight- normalized mean mirdametinib PK profile data of the PIB oral solution and the oral capsules [redacted] (b) (4) 2 mg, 1 mg) in healthy adult subjects/patients, (***ii***) the comparable mean mirdametinib PK parameter data of the oral solution and the oral capsules (1 mg, 2 mg) after a single 4 mg dose in healthy adult subjects/patients, and (***iii***) the comparable mean AUC_{0-4} and Cmax data of the oral capsules (taken whole) and the oral tablets (given as suspension) in age-matched pediatric patients in the pivotal clinical trial (SN-7 IR Response).

In Vitro Caco-2 Permeability Study

In Caco-2 Study 23SPRWP2, the apical-to-basolateral apparent permeability coefficients ($P_{app, A\rightarrow B}$) of mirdametinib at 0.332 μM and 33.2 μM dosing concentrations tested (representing 1% and 100%, respectively, based on maximum therapeutic dose of 4 mg in 250 mL) were 13.8 x 10^{-6} cm/s and 13.2 x 10^{-6} cm/s, respectively (refer to Table 6 of the study report). It is noted that these P_{app} values at both concentrations are greater than (two-fold higher than) the $P_{app, A\rightarrow B}$ of minoxidil 10 μM (the co-dosed high permeability internal standard, ~3.6 x 10^{-6} cm/s). It is also noted from the results of this uni-directional study that the Caco-2 $P_{app, A\rightarrow B}$ value at 0.332 μM dosing concentration is almost the same as that measured for 33.2 μM dosing concentration. This apparent drug concentration-independent *in vitro* drug permeation across the Caco-2 epithelium suggests that (even at the lowest initial drug concentration) passive diffusion is the predominant drug transport mechanism for mirdametinib.

Based on the results of the 1st bi-directional Caco-2 study (without co-dosed reference compounds), at 0.332 μM (the lowest drug dosing concentration evaluated in the Caco-2 study; representing the plasma C_{max} after a single 4 mg dose of the PIB oral solution), the efflux ratio is a little over 2.0 (Table 7), which suggests that the drug may be a substrate of an apical drug efflux transporter such as P-glycoprotein/P-gp at low (i.e., systemic) drug concentrations. [The proposed labeling states that mirdametinib is a substrate of drug efflux transporters (i.e., BCRP and P-glycoprotein/P-gp).] Based on the results of a 2nd bidirectional Caco-2 study (Study 764-04274, Table 1) at higher initial drug concentration, i.e., 20 μM (representing ~60% of 4 mg/250 mL mirdametinib in the gut), the efflux ratio is ~1.0, indicating that at this higher drug concentration the active drug (efflux) transporter's activity is saturated (and thus, net effect of drug efflux would be minimal). In the 3rd bidirectional Caco-2 study (24SPRWP2) submitted recently (in SN-20); the efflux ratios at mirdametinib dosing concentrations of 3.32 μM and 33.2 μM were 1.96 and 0.819, respectively. There are three lines of clinical evidence for the minimal to no effect of apical drug efflux transporters (e.g., P-gp) on mirdametinib *in vivo* absorption/bioavailability:

(1) The results of the *in vivo* human radiolabeled mass balance study indicate a high fraction absorbed (Fa) for mirdametinib.

(2) Based on the Applicant's Population PK Analysis, concomitant administration of P-gp inhibitors did not impact mirdametinib exposures in humans.

(3) In a dose-ranging PK study (Study A4581001), the exposures to the drug were observed to be dose proportional and mirdametinib PK was observed to be generally linear over the 1 mg to 20 mg dose range (which also further supports passive diffusion as the predominant transport mechanism for mirdametinib).

Note that in SN-4, the Applicant clarified that the Caco-2 permeability studies (as well as method validation) were conducted by (b) (4) Additionally, as mentioned above, the drug was shown to be stable for (b) (4) .

(b) (4)

Additional Information:

(b) (4)

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B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *Adequate*

Dissolution Method – *Acceptable*

During development, Mirdametinib Oral Capsules were tested using the dissolution method parameters in the following table.

Dissolution Medium	0.1 N HCl [redacted] (b) (4)
Apparatus	Basket Apparatus (USP/Ph. Eur. apparatus I)
Speed	75 RPM
Temperature	37°C ± 0.5°C
Vessel Volume (mL)	500 mL
Sampling Volume (mL) Sampling Timepoint (min)	5 mL 30 Minutes
Filter	10 µm cannula tip polyethylene porous filter

The capsules are wrapped in sinkers to prevent them from floating to the surface.
Sampling time points for dissolution profiling: 15, 30, 45, 60 min
3.2.P.5.2. Analytical Procedures; Dissolution Method Development Report (DMDR)

Given that mirdametinib exhibits the characteristics of a highly soluble drug substance per BCS criteria, the standard dissolution test procedure in the 2018 FDA Guidance for Dissolution Testing of Highly Soluble Drugs is applicable for the oral capsules [redacted] (b) (4) Note that the proposed basket rotation speed of 75 rpm is an acceptable speed as it is not faster than the 100 rpm speed that is recommended in the FDA Guidance for standard dissolution testing using USP Apparatus 1. The Applicant indicated that 0.1N HCl was selected [redacted] (b) (4)

In studies conducted to investigate the discriminating power of the proposed dissolution method, the dissolution profiles of the target and variant drug product lots were found to be similar within the following studied conditions/ranges: [redacted] (b) (4), (***b***) API particle size d_{90}, [redacted] (b) (4) (***c***) [redacted] (b) (4) of target levels. The anticipated rank-order relationships were observed between dissolution profiles and [redacted] (b) (4) [redacted] (b) (4) but not for API particle size. *Thus, this Assessor supports the Drug Substance Assessor's recommendation* [redacted] (b) (4) *this Biopharmaceutics Assessor does not have any concerns about the proposed API* d_{90} [redacted] (b) (4) *limit of* [redacted] (b) (4)

HPLC with UV detection at (b) (4) is used to quantify the drug in the dissolution samples. The analytical method was validated for specificity, linearity, range, accuracy, precision, robustness (with respect to dissolution method and HPLC), and solution stability. The dissolution method robustness passed the pre-specified acceptance criteria with respect to HCl concentration of the dissolution medium (0.1N (b) (4) HCl), and presence/absence of medium deaeration. Per the Drug Product Assessor, the analytical method validation for dissolution is adequate.

The Biopharmaceutics Assessor defers to the CMC Assessors for the evaluation of the Applicant's proposals (b) (4) .

(b) (4)

(b) (4) As indicated above, based on the dissolution profile and measured API d_{90} data of the clinical trial lots, this Biopharmaceutics Assessor does not have any concerns regarding the proposed API d_{90} (b) (4) tolerance limit (b) (4)

- (b) (4)

Dissolution Acceptance Criteria – *Acceptable*

Based on historical batch data (of the registration and clinical lots) and the recommendations of the 2018 FDA Guidance for Dissolution Testing of Highly Soluble Drugs, as well as ICH Q6A, the proposed dissolution acceptance criterion is 'Q = (b) (4)% at 30 min'. Based mainly on the dissolution profile (at batch release and on long-term/intermediate/accelerated stability) data of two pivotal clinical lots (1 mg CDCTX,-and 2 mg CDCTY), "Q = (b) (4)% at 30 min" is acceptable to the Biopharmaceutics Assessor.

Dissolution on Stability
During 24 months of long-term (25ºC/60% RH) and 6 months of accelerated (40ºC/75% RH) stability testing, the registration batches conformed to the proposed dissolution acceptance criterion (Q = (b) (4)% at 30 min), by USP Stage 2 (n=12) testing, with no apparent and consistent trends.

Per the Drug Product Assessor, the proposed expiration dating period of 36 months for Mirdametinib Capsules stored at 15°C-25°C in the commercial packaging configurations is acceptable.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: *Not Applicable*

The dissolution specifications of the proposed drug product are covered by the 2018 FDA Guidance on Dissolution Testing of Drug Products Containing Highly Soluble Drug Substances. The Applicant's proposed dissolution method parameters are consistent with the recommendations of this Guidance. Additionally, dissolution profile data of the pivotal clinical trial lots are available to confirm appropriateness of the proposed/standard dissolution acceptance criterion. Thus, modeling was not used to establish the clinical relevance of the dissolution method and acceptance criterion of the proposed to-be-marketed product.

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: *Not Applicable*

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

Compared to the Mirdametinib capsule lots evaluated in the pivotal Phase 2b clinical study (MEK-NF-201, ReNeu) and in primary registration/stability studies, the proposed to-be-marketed Mirdametinib Capsules have the same

formulation composition and manufacturing process, were manufactured at comparable scale by the same drug product manufacture [redacted] (b) (4), and met the same commercial QC specifications. The primary packaging of the registration batches is also the same as proposed for marketing, i.e.., HDPE bottles [redacted] (b) (4) 1 mg 40 cc with 42 tabs; 2 mg 60 cc with 42 tabs and 120 cc with 84 tabs.

However, the following quality attributes are different between the clinical/registration stability and the final to-be-marketed drug product: (***i***) appearance (in terms of capsule shell color and ink printing), and/or (***ii***) the drug substance manufacturer and/or manufacturing site changed from [redacted] (b) (4) to [redacted] (b) (4)

- Regardless of capsule appearance changes, capsule ingoing API manufacturer changes, and capsule batch size differences, all process validation/proposed commercial, registration/stability and clinical lots exhibited at least rapid dissolution (i.e., >85% dissolved within 30 min). The dissolution profiles of the process validation/proposed commercial capsule batches were similar to those of the lots used in clinical and registration/stability studies. Refer to the dissolution profile data in Table 2 and Table 5 (and other tables) of 3.2.P.5.4, as well as Figure 7 and Figure 8 of the capsule's DMDR.
- Additionally, the Applicant provided evidence of comparable dissolution profile data between capsules manufactured using the proposed commercial/clinical/registration stability and the clinical development drug substance manufacturers [redacted] (b) (4) versus [redacted] (b) (4) respectively). Refer to Figure 2 of 3.2.P.2.2.
- Furthermore, the Drug Substance Assessor confirmed that the proposed commercial API [redacted] (b) (4) process is essentially the same as used in late-stage (including the pivotal) clinical trials, the drug substance and drug product registration stability studies.

ASSESSOR NOTE (Bridging Data Between Tablets and Capsules):
According to Table 4 of 2.7.1, the only clinical study that used both Mirdametinib Tablets (0.5 mg and 1 mg) and Mirdametinib Capsules (1 mg and 2 mg) as anticancer monotherapy in the intended patient population is the pivotal Phase 2b clinical trial (Study MEK NF-201). Another Phase 2 clinical trial (Study NF-106) also used the 1 mg capsules (as monotherapy in the intended population).

In the Type C CMC WRO Meeting Minutes dated 4/9/2020, the FDA indicated no objection to the introduction of the pediatric formulation (dispersible tablets) to the ongoing pivotal clinical Study MEK-NF-201, which has been dosing patients >12 years old with the Mirdametinib Capsules.

Previously in SN-107 of the IND (139883), the Applicant reported that pediatric patients in the pivotal Phase 2 clinical trial (MEK-NF-201) exhibited preliminary PK parameters (i.e., T_{max}, C_{max}, AUC_{last}) that were similar between the capsule (1 mg and 2 mg) and tablet (b) (4) 1 mg) formulations. In SN-3 of NDA 219379, the Applicant provided clinical PK data for the final to-be-marketed dosage forms/formulations of mirdametinib from pivotal clinical Study MEK-NF-201, as recommended. Per the Applicant, in the pediatric cohort, mirdametinib PK parameters and overall exposures were generally comparable between the capsules and the tablets; refer to the tables and figures in Section 11.2.5.1.3 of the MEK-NF-201 CSR. Additionally, based on the Applicant's Population PK analyses, there was no statistically significant difference in mirdametinib exposures observed among participants who received the capsule and the tablet formulations. *Of note, the Clinical Pharmacology Assessor confirmed that in a subset of pediatric patients (in the overlapping age range of '5 to 14 years old') who received either the oral capsule or the tablet for oral suspension in the pivotal clinical trial (MEK-NF-201), the mean mirdametinib Cmax and AUC were comparable between dosage form groups.*

- Thus, because clinical PK data are already available for both the proposed commercial tablets (for suspension) and capsules, this Biopharmaceutics Assessor determined that a request to waive *in vivo* BE testing of the tablets versus capsules is not needed. Also note that in the Biopharmaceutics Information Request dated 3/27/2024 under the IND, the Sponsor was informed that per the ICH M9 Guidance, products with different dosage forms and strengths are not eligible for a BCS-based biowaiver.

Table 2 of 2.3.P (or Table 34 of 3.2.P.2.3/NDA 21379 and Table 32 of 3.2.P.2.3/NDA 217389) lists the batch numbers and other CMC information of the mirdametinib dosage forms and formulations used in clinical studies. Should bridging be required to the earlier clinical formulations/dosage forms (b) (4) clinical PK data are available for comparison.

B. 13 BIOWAIVER REQUEST

Assessment: *Not Needed*

Both 1 mg and 2 mg strengths of the proposed to-be-marketed Mirdametinib Capsules were used in the pivotal clinical trial. Thus, a biowaiver request for a proposed commercial strength not used in clinical studies is not needed.

Note that the formulation compositions of the 1 mg and 2 mg strengths of the proposed drug product are proportional to each other; refer to Table 2 of 3.2.P.5.2. Additionally, both strengths exhibit rapid to very rapid dissolution (>85% within 30 min) using the proposed QC dissolution method.

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: Not Applicable

Post-Approval Commitments

Assessment: None

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date: Gerlie Gieser, Ph.D. (12/2/2024)

Secondary Assessor Name and Date: Anitha Govada, Ph.D. (12/10/2024)

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