CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214985Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA # 214985
Assessment # 1

Drug Product Name	Daridorexant
Dosage Form	tablet
Strength	25 mg and 50 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Idorsia Pharmaceuticals Ltd
US agent, if applicable	Idorsia Clinical Development US Inc.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1; eCTD 0001	8 Jan 21	All
Supporting document 3; eCTD 0003	25 Jan 21	Drug substance (USAN name paperwork)
Supporting document 7; eCTD 0007	3 Mar 21	Facilities
Supporting document 11; eCTD 0011	23 Apr 21	Drug Product
Supporting document 13; eCTD 0013	30 Apr 21	Biopharmaceutics
Supporting document 16; eCTD 0016	28 May 21	Drug Product
Supporting document 18; eCTD 0018	11 Jun 21	Drug Product, Drug Substance
Supporting document 21; eCTD 0021	21 Jun 21	Manufacturing (process and facilities)
Supporting document 24; eCTD 0024	13 Aug 21	Drug Product

QUALITY ASSESSMENT TEAM

Reference ID: 4854289

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Zhixing Shan	Donna Christner
Drug Product	Grace Chiou	Julia Pinto
Manufacturing	Yongming Lu	Yong Hu
Microbiology	N/A	N/A
Biopharmaceutics	Kaushal Dave	Ta-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Grace Chiou	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends approval for this application based on drug substance, drug product, manufacturing (process/facilities) and biopharmaceutics reviews.

The proposed 24-month expiry is acceptable when stored at 20-25 °C.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Daridorexant is formulated as film-coated tablets containing either 25 mg or 50 mg of the active substance, daridorexant free base. (b) (4)

The proposed 24-month expiry is acceptable when stored at 20-25 °C.

Proposed Indication(s) including Intended Patient Population	for the treatment of adult patients with insomnia (b) (4)
Duration of Treatment	chronic
Maximum Daily Dose	50 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance is manufactured (b) (4) (b) (4)

The drug substance manufacturing process, characterization, release specification, container closure system and stability are satisfactory. The developed manufacturing process for the drug substance has been validated with six batches at (b) (4) kg batch scale, which demonstrates that both the process and controls are adequate to manufacture the drug substance with qualified and consistent qualities.

Based on the updated stability data obtained to date, a retest period of (b) (4) months can be granted for the drug substance, when stored at (b) (4)

Drug Product: Adequate

The excipients used in the formulation include mannitol, microcrystalline cellulose (b) (4), povidone (b) (4), (b) (4) croscarmellose sodium, magnesium stearate, silicon dioxide, and a film coat. Although this molecule is an NME, method verification by FDA Office of Testing and Research/ Division of Pharmaceutical Analysis was not requested because the method validation and stability data showed the methods are adequate. The drug product is packaged in HDPE bottles and blister packs. It is to be stored at 20-25 °C and has a proposed shelf life of 24 months. The proposed 24-month expiry is acceptable based on the data provided.

Labeling: Adequate

Manufacturing: Adequate

Process: The manufacturing process for daridorexant film-coated immediate tablets, 25 mg and 50 mg consists of the following unit operations: (b) (4)

Facility: All facilities are adequate based on previous inspection history.

Biopharmaceutics: Adequate

Dissolution Method: The provided information/data show that daridorexant is poorly soluble per the BCS criteria and exhibits pH-dependent solubility. It has a solubility of 0.188 at pH 1.2 but is insoluble at pH 4.5 and 6.8. The Applicant proposed a dissolution method [900 mL of pH 1.2 medium using USP Apparatus 2 at 75 rpm] for both strengths of the proposed drug product. The Applicant adequately justified the selection of the proposed dissolution method, including various dissolution testing conditions (apparatus, rotation speed and dissolution medium pH). In addition, the Applicant adequately demonstrated discriminating ability of the dissolution method towards change in critical material attribute (drug substance particle size), critical formulation variable (change in composition) and critical process variable ((b) (4)

Dissolution Acceptance Criterion: Based on the provided full profile dissolution data from the clinical and registration batches, the Applicant's proposed dissolution acceptance criteria of 'NLT (b) (4) (Q) at 15 minutes' for the 25 mg strength tablets, and 'NLT (b) (4) (Q) at 30 minutes' for the 50 mg strength tablets are acceptable.

Formulation Bridging: For Phase 1 and 2 clinical studies, capsule formulations (hard gelatin capsules filled with the daridorexant hydrochloride salt, ACT-541468A) and soft gelatin capsules containing its free base, ACT-541468) were used. A film-coated tablet formulation (to-be-marketed formulation) was developed for the Phase 3 program and used for Phase 1 and Phase 3 studies, as well as for the Japanese Phase 1 and Phase 2 studies.
The Applicant provided comparative dissolution profiles between the hard gelatin capsules and film-coated tablets of 25 mg strength, using the proposed dissolution method. The provided data show similar dissolution profiles between these formulations. Together with comparative dissolution profiles of 25 and 50 mg registration batches, and the rapid absorption and similar tmax values, this Reviewer concludes that the overall bridging between hard gelatin capsule used for dose-ranging and the proposed film-coated tablets of both strengths is adequate.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled by specificiation	Acceptable	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	M	Controlled by specificiation	Acceptable	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	M	Controlled by specificiation	Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled by specificiation	Acceptable	
Dissolution – BCS Class II & IV	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site	M	Controlled by specificiation	Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	IV	(b) (4)		4		
	III			4		

(b) (4)	III	(b) (4)	4		
	III		4		

Action codes for DMF Table:
1 – DMF Reviewed.
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

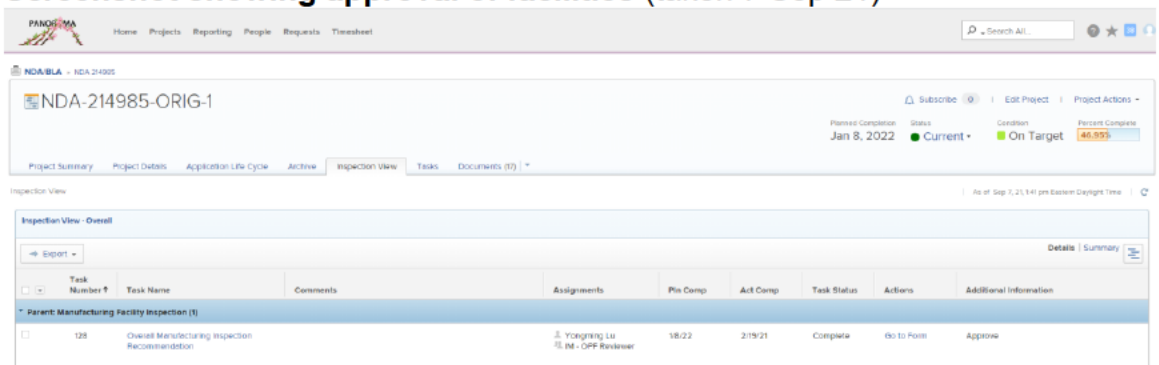
B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	128789	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

Screenshot showing approval of facilities (taken 7 Sep 21)



Valerie Amspacher

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

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 Established name(s) Route(s) of administration	Quviviq (daridorexant) tablets, for oral use, controlled substance symbol	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 25 mg, 50 mg.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	NA	NA

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Reference ID: 4854289

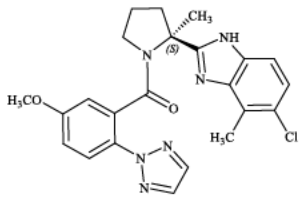
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	NA	NA

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Reference ID: 4854289

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s) Strength(s) in metric system If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	QUVIVIQ (daridorexant) tablets are available as: 25 mg: light purple, arc-triangle shaped, film-coated tablet debossed with "25" on one side and "i" (Idorsia logo) on the other side. 50 mg: light orange, arc-triangle shaped, film-coated tablets debossed with "50" on one side and "i" (Idorsia logo) on the other side.	Inadequate Per USP salt policy, revise to include a salt equivalency statement.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s) Dosage form(s) and route(s) of administration If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance. List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	QUVIVIQ contains daridorexant hydrochloride, an orexin receptor antagonist. The chemical name of daridorexant hydrochloride is (S)-(2-(5-chloro-4-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride. The molecular formula is $C_{23}H_{23}N_6O_2Cl$ * HCl. The molecular weight is 487.38 g/mol. The structural formula is:  Daridorexant hydrochloride is a white to light yellowish powder that is very slightly soluble in water. QUVIVIQ tablets are intended for oral administration. Each film-coated tablet contains 27 mg or 54 mg of daridorexant hydrochloride equivalent to 25 mg or 50 mg of daridorexant. The inactive ingredients are: mannitol, microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate, and silicon dioxide. In addition, the film coating contains the following inactive ingredients: hypromellose, microcrystalline cellulose, glycerin, talc, titanium dioxide, iron oxide red, iron oxide black, and in the 50 mg tablet only, iron oxide yellow.	Inadequate Revise to ensure all excipients are in alphabetical order.

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.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ therapeutic class	See above	Adequate
Chemical name, structural formula, molecular weight	See above	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	See above	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	NA

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Reference ID: 4854289

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) Strength(s) in metric system Available units (e.g., bottles of 100 tablets) Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	QUVIVIQ tablets are available as: • 25 mg, light purple, arc-triangle shaped film-coated tablets debossed with "25" on one side, and "i" (Idorsia logo) on the other side. NDC 80491-7825-3, bottle of 30 with child-resistant closure • 50 mg: light orange, arc-triangle shaped film-coated tablets debossed with "50" on one side, and "i" (Idorsia logo) on the other side. NDC 80491-7850-3, bottle of 30 with child-resistant closure	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	NA	NA

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

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.)	NA	NA
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.”	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].	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.”	NA	NA
Include information about child-resistant packaging	Not present	Inadequate Revise to include child-resistant packaging statement.

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Reference ID: 4854289

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 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	Distributed by: **Idorsia Pharmaceuticals US Inc.** One Radnor Corporate Center, Suite 101 100 Matsonford Rd Radnor, PA 19087	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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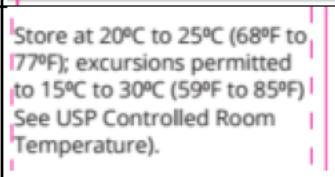
Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Quviviq (daridorexant) 25 mg tablets For oral administration	Adequate
Dosage strength		
Route of administration		
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each tablet contains: daridorexant…. 25 mg (equivalent to 27 mg daridorexant hydrochloride)	Adequate
Net contents (e.g. tablet count)	30 tablets	Adequate
"Rx only" displayed on the principal display	Rx only	Adequate
NDC number		Adequate
Lot number and expiration date		Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.		Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA

Bar code		Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Distributed by Idorsia Pharmaceuticals US Inc. Radnor, PA 19087	Adequate
Medication Guide (if applicable)	See below	Adequate
No text on Ferrule and Cap overseal	None present	Adequate
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.	NA	NA
And others, if space is available	NA	NA

Assessment of Carton and Container Labeling:
Adequate, pending the Applicant's acceptance of the revisions noted above in red.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

See below

Overall Assessment and Recommendation:

This application is recommended for approval per labeling/labels perspective once the following changes have been made to the label.

Grace Chiou

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Julia Pinto

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BIOPHARMACEUTICS

Application No: NDA 214985; 505(b)(1)
Drug Product Name/Strengths: QUVIVIQ™ (daridorexant) Tablets; 25 mg, 50 mg
Route of Administration/Dosage Form: Oral/ Immediate-Release Tablets
Indication: Treatment of adult patients with insomnia (b) (4)

Applicant Name: Idorsia Pharmaceuticals Ltd
Date of Submission: 01/08/2021 (Original)
Primary Reviewer: Kaushalkumar Dave, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.
Review Recommendation: Adequate

EXECUTIVE SUMMARY

Submission: The proposed drug product, QUVIVIQ™ (daridorexant) Tablets (referred by the Applicant as ACT-541468), 25 mg and 50 mg, submitted under 505(b)(1), is an immediate-release dosage form for oral administration indicated for the treatment of insomnia. The clinical development program comprises eighteen clinical pharmacology studies and five clinical studies in subjects with insomnia. The evidence of the efficacy and safety of daridorexant in the treatment of patients with insomnia is primarily derived from two Phase 3 studies (ID-078A301 and ID-078A302), one ongoing Phase 3 extension study (ID-078A303) and two Phase 2 dose-finding studies (AC-078A201 and AC-078A202). The Applicant studied both strengths, 25 mg and 50 mg, of the proposed drug product in clinical studies and therefore a biowaiver request is neither submitted nor required. Per the labeling, the recommended dosage of QUVIVIQ™ is 50 mg once per night, taken orally within 30 minutes before going to bed.

Dissolution Method: The provided information/data show that daridorexant is poorly soluble per the BCS criteria and exhibits pH-dependent solubility. It has a solubility of 0.188 at pH 1.2 but is insoluble at pH 4.5 and 6.8. The Applicant proposed a dissolution method [900 mL of pH 1.2 medium using USP Apparatus 2 at 75 rpm] for both strengths of the proposed drug product. The Applicant adequately justified the selection of the proposed dissolution method, including various dissolution testing conditions (apparatus, rotation speed and dissolution medium pH). In addition, the Applicant adequately demonstrated discriminating ability of the dissolution method towards change in critical material attribute (drug substance particle size), critical formulation variable (change in composition) and critical process variable ((b) (4) . Based on the provided information/data, the proposed dissolution method is deemed adequate for QC testing of the proposed drug product.

Dissolution Acceptance Criterion: Based on the provided full profile dissolution data from the clinical and registration batches, the Applicant's proposed dissolution acceptance criteria of 'NLT (b) (4)% (Q) at 15 minutes' for the 25 mg strength tablets, and 'NLT (b) (4)% (Q) at 30 minutes' for the 50 mg strength tablets are deemed acceptable for QC testing of the proposed drug product with the proposed dissolution method at batch release and during stability testing.

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Formulation Bridging: For Phase 1 and 2 clinical studies, capsule formulations (hard gelatin capsules filled with the daridorexant hydrochloride salt, ACT-541468A) and soft gelatin capsules containing its free base, ACT-541468) were used. A film-coated tablet formulation (to-be-marketed formulation) was developed for the Phase 3 program and used for Phase 1 and Phase 3 studies, as well as for the Japanese Phase 1 and Phase 2 studies.

The Applicant provided comparative dissolution profiles between the hard gelatin capsules and film-coated tablets of 25 mg strength, using the proposed dissolution method. The provided data show similar dissolution profiles between these formulations. Together with comparative dissolution profiles of 25 and 50 mg registration batches, and the rapid absorption and similar t_{max} values, this Reviewer concludes that the overall bridging between hard gelatin capsule used for dose-ranging and the proposed film-coated tablets of both strengths is adequate.

RECOMMENDATION

From a Biopharmaceutics perspective, NDA 214985 for QUVIVIQ™ (daridorexant) Tablets, 25 mg and 50 mg, is **adequate** and recommended for **approval**.

FDA-approved dissolution method and acceptance criteria for batch release and stability testing of both strengths of the proposed product

Apparatus	USP Apparatus 2 (Paddle)
Paddle Speed	75 rpm
Volume	900 mL
Medium	pH 1.2 Medium (NaCl/HCl)
Temperature	37.0 ± 0.5 C
Acceptance Criterion	25 mg strength: Q = (b) (4) at 15 minutes 50 mg strength: Q = at 30 minutes

Reference ID: 4854289

BIOPHARMACEUTICS ASSESSMENT

LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	**Received date**	**Document**
0001	01/08/2021	Original NDA Submission
0013	04/30/2021	Quality/Response to Information Request

DRUG SUBSTANCE AND DRUG PRODUCT

Daridorexant (ACT-541468) is a potent and selective dual orexin receptor antagonist that inhibits the actions of orexin neuropeptides at both OX1 and OX2 receptors and has been developed for the treatment of insomnia disorder. Daridorexant free base is a poorly soluble (logP = 3.9) drug substance developed for the treatment of insomnia. Due to the indication, the Applicant chose to develop an immediate release (IR) dosage form to ensure faster solubilization and absorption of the drug upon administration. The Applicant studied various IR dosage forms during the early phases of the development. However, a film-coated IR tablet was used in the (pivotal) Phase 3 study and is the proposed to-be-marketed drug product. The composition of the proposed drug product is as follows:

Table 1 Composition of 25 and 50 mg daridorexant tablets

Dose strength		25 mg	50 mg
	Ingredient function	**Quantity per film-coated tablet**	**Quantity per film-coated tablet**
			(b) (4)

***BCS Designation* - None**

Solubility

The Applicant studied the solubility of daridorexant across the physiological pH range (pH 1.2~6.8). The results of the experimental solubility study, summarized in Table 1, indicate that daridorexant is a poorly soluble drug substance, per the BCS criteria, and exhibits pH dependent solubility. It has a solubility of 0.188 at pH 1.2 but is insoluble at pH 4.5 and 6.8.

Table 2: Aqueous solubility of daridorexant

Buffer	Concentration of daridorexant after 24 hours (mg/mL)		Concentration of daridorexant after 26 hours (mg/mL)	
pH=1.2 (n = 3)	0.188	Mean: 0.188	0.188	Mean: 0.188
	0.188		0.188	
	0.189		0.188	
pH=4.5 (n = 3)	0.002	Mean: 0.002	0.002	Mean: 0.002
	0.001		0.002	
	0.002		0.002	
pH=6.8 (n = 3)	0.001	Mean: 0.001	0.001	Mean: 0.001
	0.001		0.001	
	0.001		0.001	

The Applicant observed that at pH 4.5 and 6.8 daridorexant hydrochloride stayed on top of the media due to its poor wettability. This explains the very low amount of drug substance dissolved under these conditions compared to acidic conditions.

Permeability

The Applicant stated in the submission that daridorexant is a BCS Class 2 drug. However, no information of permeability of the drug substance was provided for this application.

It is important to note that no BCS designation request has been submitted by the Applicant and no designation has been determined by the FDA for daridorexant.

Dissolution Method Development

The Applicant's proposed dissolution method and acceptance criterion are as follow:

Table 3: Applicant's proposed dissolution method and acceptance criterion

Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	75 rpm
Volume	900 mL
Medium	pH 1.2 Medium (NaCl/HCl)
Temperature	37.0 ± 0.5°C
Acceptance Criterion	25 mg Tablets: Q = (b) (4)% at 15 minutes 50 mg Tablets: Q = % at 30 minutes

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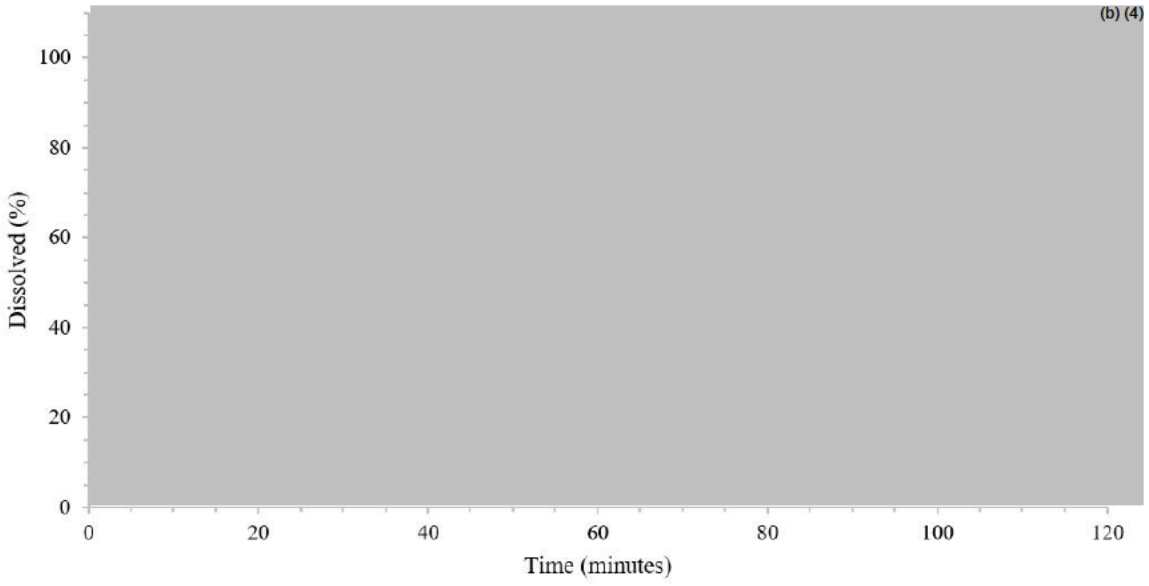
Discriminating Ability of the Dissolution Method

Impact of particle size distribution of the drug substance as a critical material attribute on dissolution of 10, 25 and 50 mg tablets using the proposed quality control (QC) method was investigated by comparing batches manufactured with (b) (4) (Table 5). Results of the study are illustrated in Figure 4 and Figure 5.

Table 5. Descriptions of (b) (4) drug substance batches used for dissolution comparisons

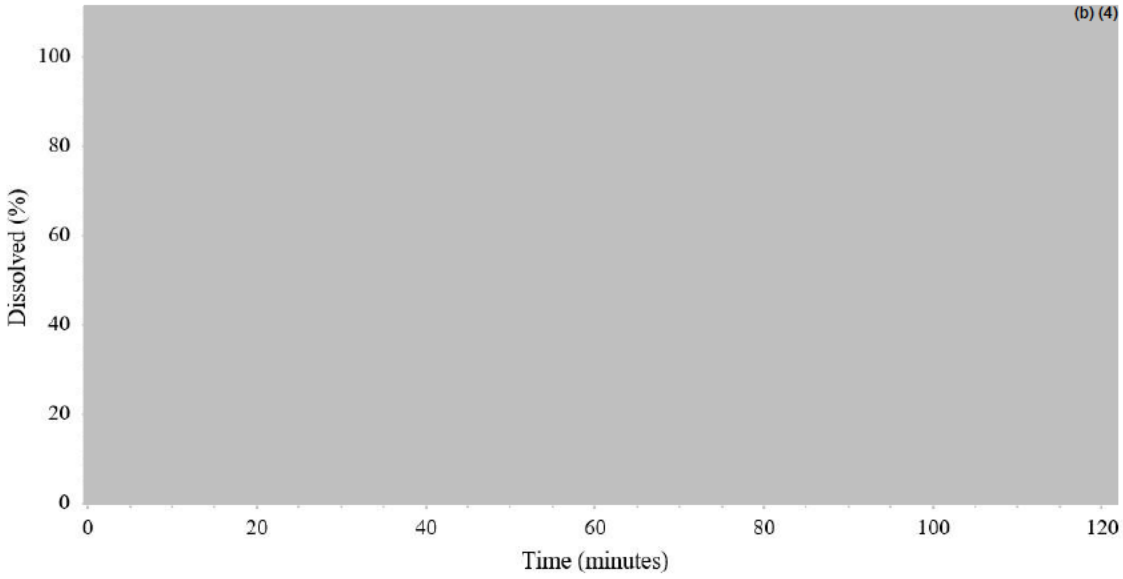
Drug substance batch number	**RH04L117A1** (b) (4)	**RH04L117A0** (b) (4)
Manufacturer	(b) (4)	
Manufacturing date	January 2016	January 2016
Particle size distribution	Diameter	Diameter
10^{th} percentile	(b) (4)	(b) (4)
50^{th} percentile		
90^{th} percentile		

Figure 4. Comparison of dissolution profile of 25 mg tablets (b) (4)



Reference ID: 4854289

Figure 5. Comparison of dissolution profile of 50 mg tablets (b) (4)



The provided data show significant difference in drug release profiles between the drug products (b) (4) for both proposed strengths. Note that the proposed dissolution method is shown to be discriminating toward the drug substance particle size with the proposed dissolution acceptance criterion (Q (b) (4) % at (b) (4) min) for the proposed two strengths.

Furthermore, the Applicant tested the discriminating ability of the proposed dissolution method toward formulation and process changes as described in Table 6 and Table 7. The results of these studies are presented in Figure 6 and Figure 7.

Table 6. Deviant batches of 25 mg tablets used for testing discriminating ability of the proposed dissolution method

Tablet batch number	**17.112.077 (25 mg tablets reference)**	**17.112.047 (formulation and process changes)**	**17.112.058 (formulation and process change)**
Manufacturer	(b) (4)		
Manufact. date	July 2017	March 2017	May 2017
Purpose	Technical batch	Technical batch	Technical batch
Changes compared to reference (Batch 17.112.077)	(b) (4)		

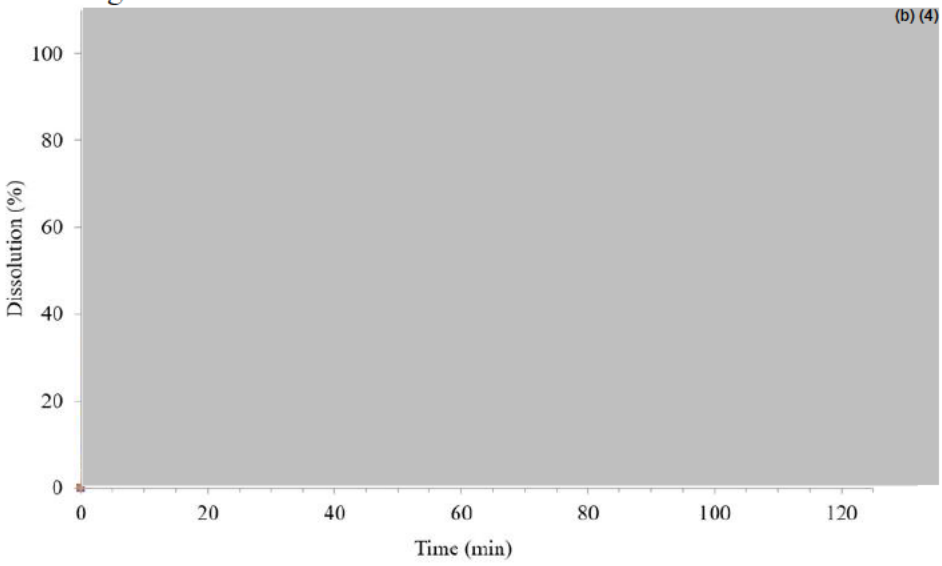
Reference ID: 4854289

Tablets batch number	17.112.079	17.112.085	17.112.086 (Process change)
Manufacturer	(b) (4)	(b) (4)	(b) (4)
Manufact. date	August 2017	September 2017	September 2017
Purpose	Technical batch	Technical batch	Technical batch
Changes compared to reference	(b) (4)		

Table 7. Deviant batches of 50 mg tablets used for testing discriminating ability of the proposed dissolution method

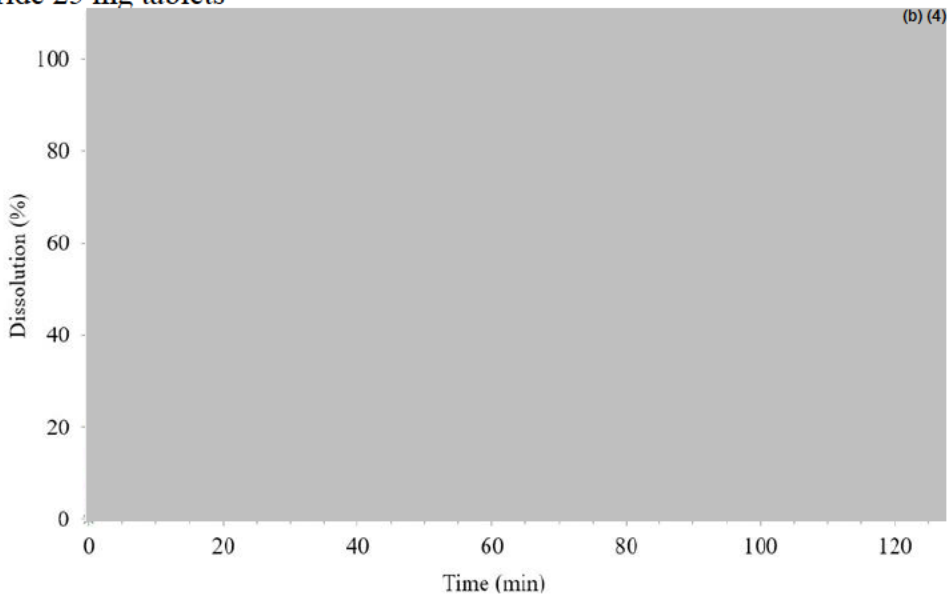
Tablet batch number	17.112.088A	17.112.087	17.112.080ter (Process change)
Manufacturer	(b) (4)	(b) (4)	(b) (4)
Manufact. date	October 2017	October 2017	September 2017
Purpose	Technical batch	Technical batch	Technical batch
Changes to ref.	(b) (4)		

Figure 6. Impact of formulation and process changes on the dissolution profiles of daridorexant hydrochloride 25 mg tablets



Reference ID: 4854289

Figure 7. Impact of API and process changes on the dissolution profiles of daridorexant hydrochloride 25 mg tablets



The provided data show that the proposed dissolution method can detect changes in the drug product composition as well manufacturing process (b) (4)). With the proposed dissolution method and acceptance criterion, deviant batches of Daridorexant Tablets, 25 mg and 50 mg, will fail in QC dissolution testing. This Reviewer determines that the provided data were adequate and have demonstrated that the proposed dissolution method is discriminating toward change in critical material attributes, critical formulation variables and critical process parameters. The proposed dissolution method is deemed adequate for QC testing of the proposed drug product.

Dissolution Acceptance Criteria

Full-profile numerical data for clinical and registration batches collected at the time of batch release and during stability were provided (response to an IR dated 04/30/2021), in addition to mean dissolution profiles of all registration batches provided in the original submission.

Table 8. Description of Clinical Batches

Strength	Batch number	Batch size (approx.)	Month of manufacture	Study
10 mg	**1 (10 mg)**	(b) (4)	Nov 2017	Phase 3
10 mg	**2-1 (10 mg)**		Mar 2018	Phase 3
10 mg	**8 (10 mg)**		Oct. 2019	Phase 3
25 mg	**1 (25 mg)**		Nov 2017	Phase 3
25 mg	**3 (25 mg)**		May 2018	Phase 3
25 mg	**8 (25 mg)**		Oct. 2019	Phase 3
50 mg	**1 (50 mg)**		Nov 2017	Phase 3
50 mg	**2 (50 mg)**		Mar 2018	Phase 3
50 mg	**7 (50 mg)**		Oct. 2019	Phase 3

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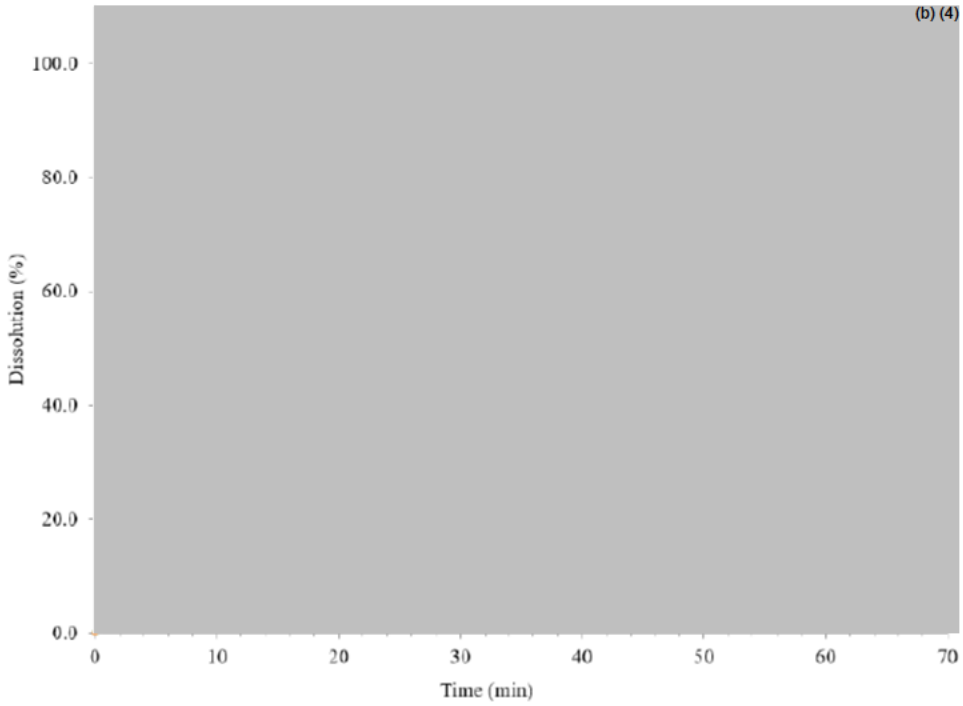
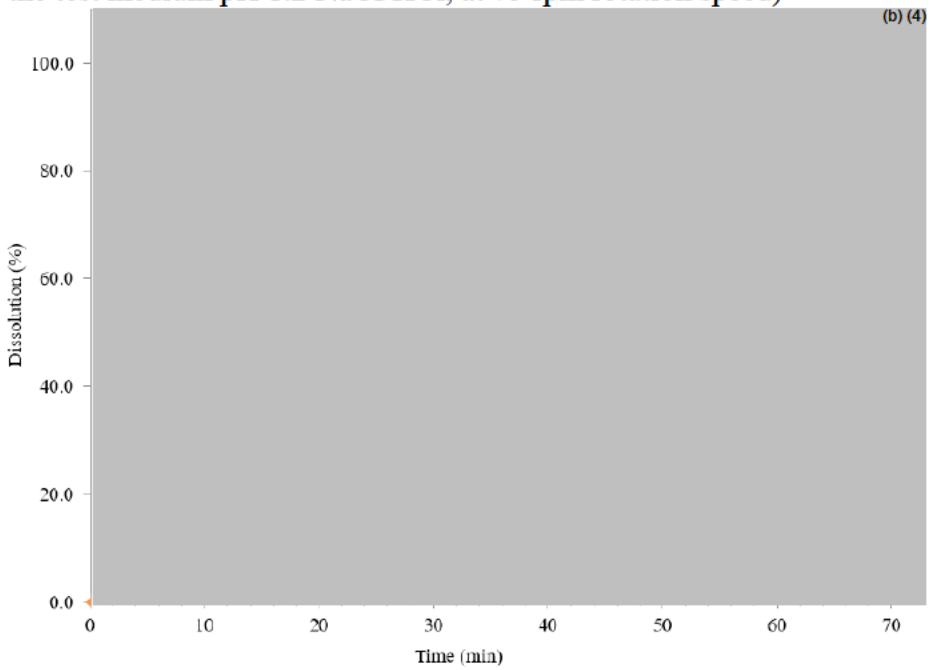
Dissolution profiles (n = 12) of these pivotal batches (Table 8) and registration batches were generated at release using the QC method (Paddle, 75 rpm, 37 °C, pH 1.2 NaCl/HCl). Mean dissolution data for the pivotal batches and registration batches are presented in Figure 7 and Figure 8, respectively.

Figure 7. Dissolution profiles of 10, 25, and 50 mg pivotal batches at release (n = 12, paddle, 37 °C, with the test medium pH 1.2 NaCl/HCl, at 75 rpm rotation speed)



Reference ID: 4854289

Figure 8. Dissolution profiles of 25 and 50 mg registration batches at release (n = 12, paddle, 37 °C, with the test medium pH 1.2 NaCl/HCl, at 75 rpm rotation speed)



The provided dissolution profile data indicate that the Applicant's proposed dissolution acceptance criterion are data-driven and appropriately selected. Together with the proposed method that is discriminating, the Applicant's proposed dissolution acceptance criterion is deemed adequate for QC testing of the proposed drug product.

In response to an IR, the Applicant submitted (on 04/30/2021) full drug release profiles of registration batches for both the strengths of the proposed drug product for long-term testing up to 12 months (and accelerated stability under 40°C/75% RH condition for 6 months). The provided stability data show consistent dissolution profiles and no significant trend in drug release was observed during the stability period. The accepted strength-dependent dissolution acceptance criteria are adequate for QC testing of the proposed drug product for batch release and stability testing.

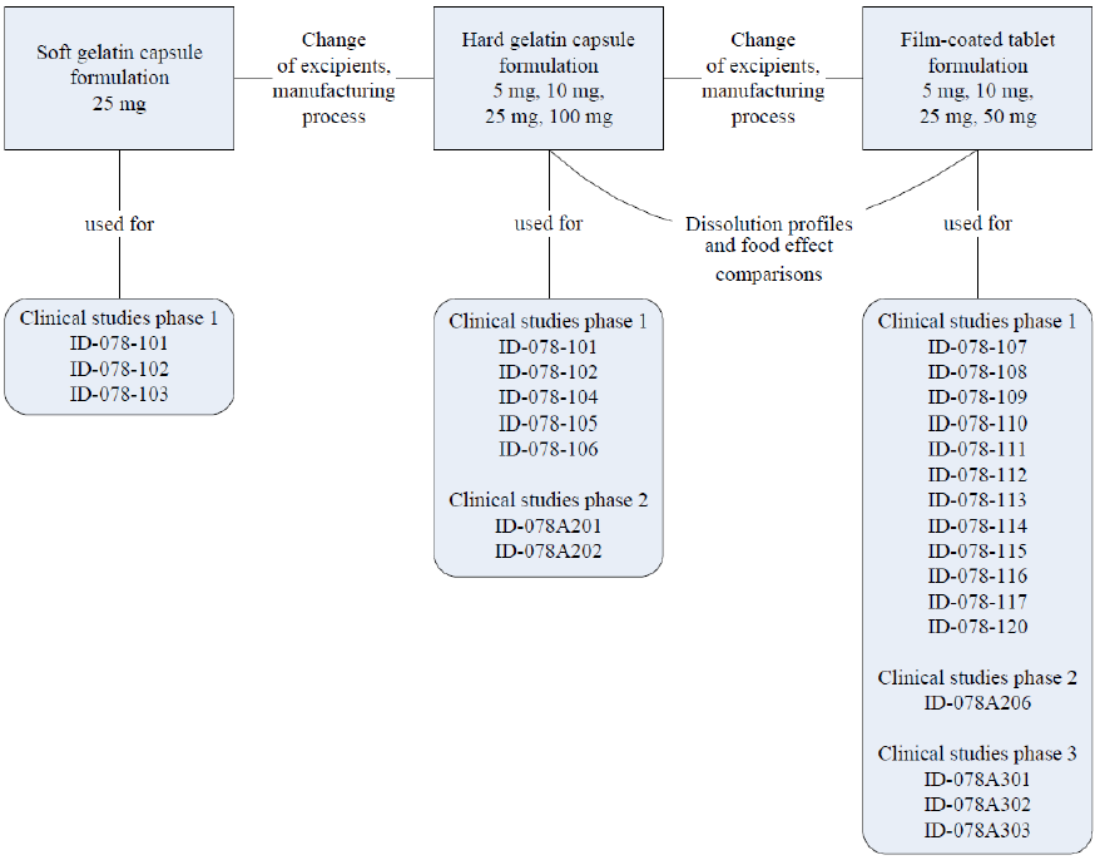
Formulation Bridging

Three oral formulations of daridorexant were developed and evaluated during the development program (Figure 9), briefly:

- A hard gelatin capsule (filled with the daridorexant hydrochloride salt, ACT-541468A) used in Phase 1 and Phase 2 clinical studies until the start of the Phase 3 program. Note that only 25 mg strength capsule was used in Phase 1 and Phase 2 (dose-ranging) studies.
- A soft gelatin capsule (containing its free base, ACT-541468) evaluated in the first few clinical pharmacology studies only.
- A film-coated tablet (containing ACT-541468A) intended for commercial use, which was used in Phase 1, Japanese Phase 1 and 2, and Phase 3 clinical studies.

Reference ID: 4854289

Figure 9. Overview of formulations used in clinical studies

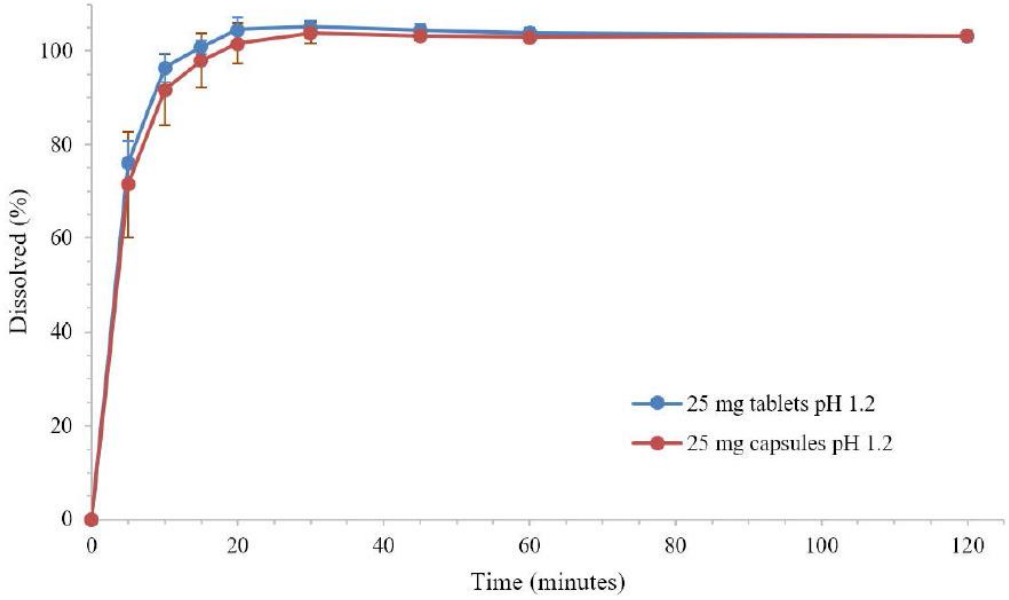


The Applicant studied comparative PK and PD profiles of the soft gelatin capsules and hard gelatin capsules under the clinical study in AC-078-101. In an E-Mail communication (dated 08/31/2021) with the Clinical Pharmacology Reviewer, Dr. Praveen Balimane, it was confirmed that results from studies conducted with the prior developmental formulations will not be used in support of the labeling. However, it is noted that only the 25 mg strength hard gelatin capsule was used in Phase 1 and Phase 2 (dose-ranging) studies, thus it is necessary to bridge hard gelatin capsule to the proposed film-coated tablet of both strengths.

The Applicant provided comparative dissolution profiles between the hard gelatin capsules and film-coated tablets of 25 mg strength, using the proposed dissolution method. The provided data show similar dissolution profiles between these formulations (Figure 10). Together with comparative dissolution profiles of 25 and 50 mg registration batches as presented in Figure 8, and the rapid absorption and similar t_{max} values, this Reviewer concludes that the overall bridging between hard gelatin capsule used for dose-ranging and the proposed film-coated tablets of both strengths is adequate.

Reference ID: 4854289

Figure 10. Dissolution profile of daridorexant film-coated tablets and hard gelatin capsules at 25 mg dose strength in buffer pH 1.2, USP apparatus II, 75 rpm (n = 12)



Biowaiver Request

The Applicant included both strengths of the proposed product in clinical studies. Biowaiver request is not needed or submitted.

Kaushalkumar Dave

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Ta-Chen Wu

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Valerie Amspacher

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Date: 9/09/2021 12:45:07PM
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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