CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209203Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 209203
Review #1

Drug Name/Dosage Form	Lesinurad/allopurinol tablets
Strength	200/200 & 200/300 mg lesinurad/allopurinol
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Ardea Biosciences, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	*20-OCT-2016*	*all*
Amendment	*12-JAN-2017*	*process*
Amendment	*02-FEB-2017*	*biopharmaceutics*
Amendment	*09-MAR-2017*	*drug product*
Amendment	*28-MAR-2017*	*biopharmaceutics*
Amendment	*06-APR-2017*	*process*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joe Leginus	NDBII/DNDAPI
Drug Product	Chris Hough	NDPBIV/DNDPII
Process	Chaoying Ma	PABIV/DPAII
Microbiology	Chaoying Ma	PABIV/DPAII
Facility	Christina Capacci-Daniel	IABII/DIA
Biopharmaceutics	Poonam Delvadia	BBIII/DB
Regulatory Business Process Manager	Florence Aisida	RBPMBI/DRBPMI
Application Technical Lead	Craig M. Bertha	NDPBIV/DNDPII
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)		

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Review Complete Date	Comments
(b) (4)	III		(b) (4)	Not reviewed		Sufficient information in NDA
	III			Not reviewed		Sufficient information in NDA
	III			Not reviewed		Sufficient information in NDA
	III			Not reviewed		Sufficient information in NDA
	III			Not reviewed		Sufficient information in NDA
	III			Not reviewed		Sufficient information in NDA
	III			Not reviewed		Sufficient information in NDA
	III			Not reviewed		Sufficient information in NDA
	III			Not reviewed		Sufficient information in NDA
	II			Adequate	23-JAN-2017	
	IV			Not reviewed		Sufficient information in NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	102128	Ardea's lesinurad tablets
IND	119031	Ardea's lesinurad/allopurinol tablets
NDA	207988	Ardea's lesinurad tablets

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the reviews and recommendations from the drug substance, drug product, biopharmaceutics, process, and facilities teams outlined in the review below, an overall recommendation of **approval** is being forwarded to the clinical Division (DPARP). A 24 month expiration dating period is granted for the drug product.

II. Summary of Quality Assessments

A. Product Overview

The current application seeks approval for the fixed-dose combination tablet drug product for treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with allopurinol alone. There are two strength fixed-dose combinations for once-daily dosing.

Proposed Indication(s) including Intended Patient Population	Hyperuricemia
Duration of Treatment	(b) (4)
Maximum Daily Dose	200/300 mg lesinurad/allopurinol
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

The tablet drug product is a fixed dose combination of lesinurad, a URAT1 inhibitor, and allopurinol, a xanthine oxidase inhibitor (XOI), and is indicated for the (b) (4) treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with allopurinol alone.

The lesinurad drug substance information for this application was provided by reference to the applicant's approved NDA 207988 for lesinurad tablets. Information for the allopurinol was provided by letter authorization to allow reference to (b) (4) type II DMF (b) (4). Refer to the reviews for those documents for information about the CMC for the two drug substances.

Lesinurad is a BCS class II compound and allopurinol is a BCS class IV compound. PSD for Allopurinol is controlled at D(v,0.5) NMT (b) (4) microns, and PSD for Lesinurad is

controlled at NMT [redacted] microns. Lesinurad is reported to possess two known [redacted] crystal forms [redacted] polymorphs), and other [redacted].

The applicant supports two fixed-dose combinations (FDC) of 200/200 mg and 200/300 mg of lesinurad/allopurinol. These are light and dark orange debossed film coated tablets, respectively. The tablets include lactose, cellulose, hypromellose, crospovidone, and magnesium stearate as excipients. In both formulations, the % w/w for both APIs is greater [redacted]%, thus achieving content uniformity is not difficult. This combination lesinurad/allopurinol tablet meets all of the quality standards targeted for it in its specification. The two different strengths are easily distinguished. The strengths of the two actives are well controlled, as are the excipients. The finished product in the commercial container-closure is stable enough to meet its specification at 24 months.

The drug product manufacturing process includes [redacted] The proposed in-process controls include [redacted] Batch AAAD for the 200/200 mg formulation, and batch SAAD for the 200/300 mg formulation, have been manufactured and used for the bioavailability studies.

The range of [redacted] batch size is approximately [redacted] kg, which corresponds to approximately [redacted] tablets. For the maximum [redacted] batch size of [redacted] kg, three (3) [redacted] batches are manufactured, [redacted] The [redacted] tablet [redacted] film coated up to a [redacted]

The proposed dissolution method, discriminating ability of the method, dissolution acceptance criterion, dissolution analytical method, PBPK modeling and simulation in support of the proposed PSD of both drugs and wider dissolution acceptance criterion for lesinurad, *in vitro* bridging for change in non-functional film coating for the proposed FDC IR tablet, were reviewed in detail and were found to be adequate. The Applicant adequately responded to the two biopharmaceutics information requests and PBPK questions discussed during the teleconference on 06-JUL-2017. It should be noted that although the proposed PBPK model is considered adequate for supporting PSD of drugs and wider dissolution acceptance criterion for lesinurad, further refinement of this model would be required if it were later proposed to broaden its application for lifecycle management (see letter to the applicant dated 20-JUL-2017).

There are five facilities associated with drug substance manufacture and three supporting drug product manufacture. The facilities team has found these to be adequate after a review of application and inspection documentation.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

56 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER IV: Labeling

APPEARS THIS WAY ON ORIGINAL

LABELING

{For NDA only}

R Regional Information

1.14 Labeling

Physician's Insert

Additions are in red.

3 DOSAGE FORMS AND STRENGTHS

TRADENAME is a combination of lesinurad and allopurinol. TRADENAME tablets are available in the following oral dosage forms and strengths:

- 200 mg/200 mg, capsule-shaped tablets are light orange film coated tablets debossed with "LES200" above "ALO200".
- 200 mg/300 mg, capsule-shaped tablets are dark orange film coated tablets debossed with "LES200" above "ALO300".

11 DESCRIPTION

TRADENAME (lesinurad and allopurinol) capsule-shaped tablets contain 2 oral medications used in the treatment of hyperuricemia: lesinurad and allopurinol. Lesinurad is a URAT1 inhibitor and allopurinol is a xanthine oxidase inhibitor.

Lesinurad

Lesinurad has the following chemical name: 2-((5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetic acid. The molecular formula is $C_{17}H_{14}BrN_3O_2S$ and the molecular weight is 404.28. The structural formula is:

Table 1: TRADENAME Tablet Presentations

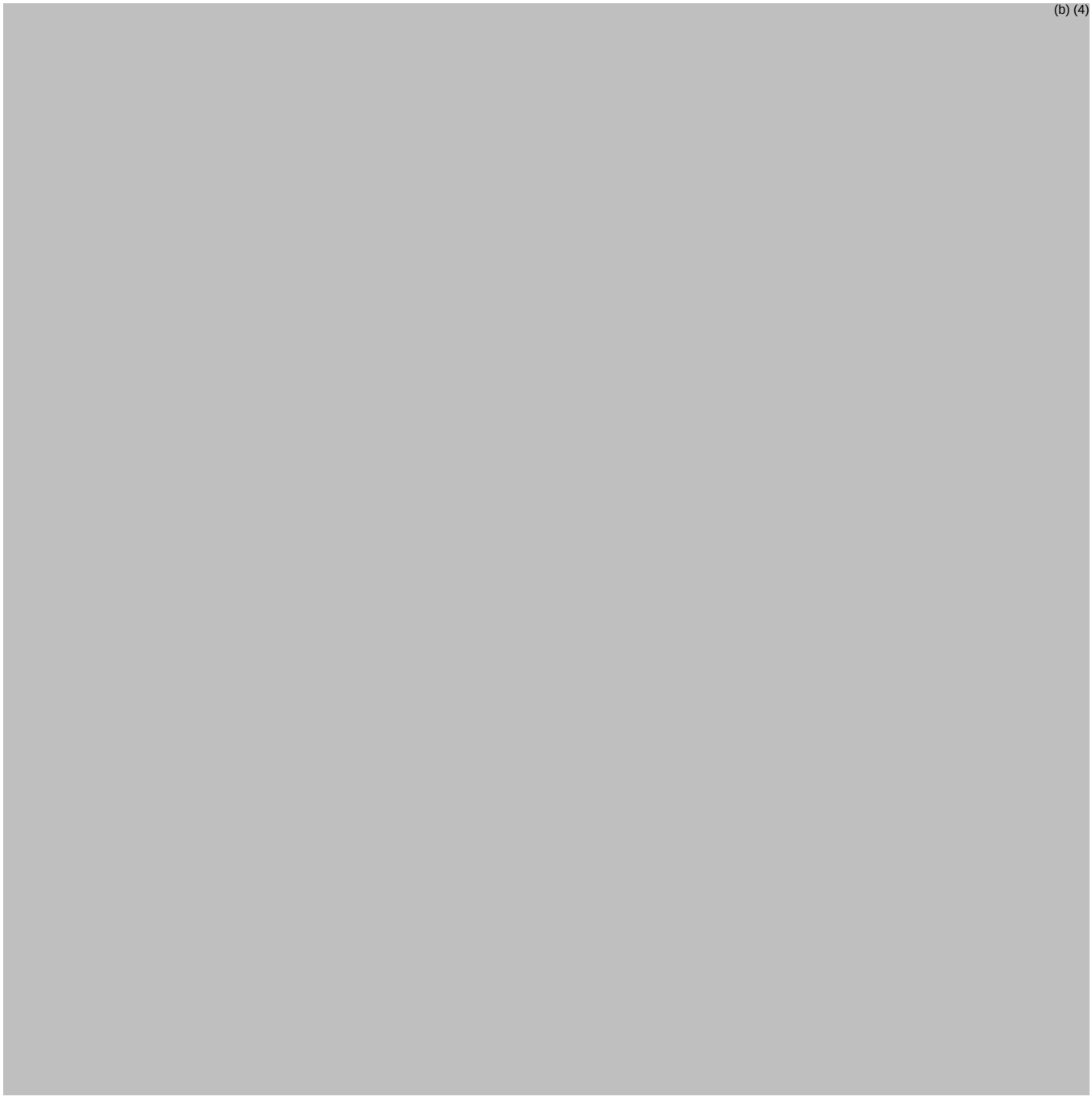
Tablet Strength **(Lesinurad/Allopurinol)**	**Film-Coated Tablet**	**Tablet Markings**	**Pack Size**	**NDC Code**
200/200 mg	Light orange film coated, capsule-shaped tablet	Debossed with "LES200" above "ALO200"	Bottle of 5 tablets Bottle of 30 tablets Bottle of 90 tablets	XXXXXXX
200/300 mg	Dark orange film coated, capsule-	Debossed with "LES200" above	Bottle of 5 tablets	XXXXXXX

	shaped tablet	“ALO300”	Bottle of 30 tablets Bottle of 90 tablets	

16.2 Storage and Handling

(b) (4). Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F) [*see USP Controlled Room Temperature*].

Immediate Container Label



(b) (4)

Reviewer's Assessment: *All regulatory requirements from a CMC perspective have been satisfied.*

Reviewer's Assessment: *No carton label was presented.*

List of Deficiencies:

Primary Labeling Reviewer Name and Date: Christopher Hough, Ph.D.

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Julia Pinto

Digitally signed by Julia Pinto
Date: 6/28/2017 10:48:08AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

Christopher Hough

Digitally signed by Christopher Hough
Date: 6/27/2017 03:05:52PM
GUID: 508da7220002a180df90e5ffe899ce1f

BIOPHARMACEUTICS

NDA: NDA-209203-ORIG-1

Applicant Name: Ardea Biosciences Inc.

Type of NDA: 505(b)(2) Submission

Drug Product Name: DUZALLO (Lesinurad/Allopurinol) Fixed-Dose Combination (FDC) Tablets

Dosage Form: Immediate Release (IR) Tablets

Strength(s): 200mg/200mg; and 200mg/300mg

Route of Administration: Oral

Indication: Lesinurad (a URAT1 inhibitor) and allopurinol (a xanthine oxidase inhibitor) is indicated for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with allopurinol alone[1]. (b) (4)

Reference Drug:
Zurampic® (lesinurad) tablets, for oral use (NDA 207988; Approved on December 22, 2015)
Zyloprim® (allopurinol) tablets, for oral use (NDA 016084; Approved on August 19, 1966)

Compositional Proportionality of Strengths (According to the Applicant): Both proposed strengths, 200mg/200mg and 200mg/300mg, are proportionally similar according to the Applicant. However, as communicated by FDA in Type-C investigational new drug (IND) meeting, (b) (4)

The Applicant has conducted pivotal bioequivalence (BE) studies for the proposed product comparing it to the reference drug product on both strengths.

[1] Global Submit – N209203 - 0000(1) dated 10/20/2016. Module 1.14.1.3. Draft Labeling Text - PDF. (Accessed on July 07, 2017)
[2] Global Submit – N209203 - 0000(1) dated 10/20/2016. Module 1.6.3. Correspondence Regarding Meetings - Type-C Meeting Minutes 19 Jan 2016. (Accessed on July 07, 2017)

The recommended dose of the proposed product is one 200mg lesinurad/300mg allopurinol tablet per day (or one 200mg lesinurad/200mg allopurinol for patients with renal impairment). (b) (4) . The proposed tablets should be taken in the morning with food and water as per labeling.

The proposed lesinurad/allopurinol 200/200 FDC tablet is light orange, capsule-shaped, film-coated tablets (7.14 x 17.15 mm) debossed with LES200 above ALO200 on one side and the other side of the tablet is blank. The proposed lesinurad/allopurinol 200/300 FDC tablet is dark orange, capsule-shaped, film-coated tablets (7.82 x 18.67 mm) debossed with LES200 above ALO300 on one side and the other side of the tablet is blank.[3] The FDC tablets will be available in bottle count of 5, 30 and 90. The qualitative and quantitative composition of the proposed lower (200mg/200mg) and higher (200mg/300mg) strengths FDC tablets is provided in Table 1.[3] The proposed lesinurad/allopurinol FDC tablets are manufactured using (b) (4) pharmaceutical manufacturing process that includes (b) (4)

Table 1. Formulation Composition of Lesinurad/Allopurinol 200/300 (Left) and 200/200 (Right) FDC Tablets

Component Name	Quality Standard	Function	Quantity per Unit (mg)	% w/w
(b) (4)				
Lesinurad	In-house	Active ingredient	200.00	(b) (4)
Allopurinol[3]	USP	Active ingredient	300.00	
Lactose Monohydrate	NF			(b) (4)
Microcrystalline Cellulose	NF			
Crospovidone	NF			
Hydroxypropyl Cellulose	NF			
(b) (4)				
Film Coating				
Opadry Beige (b) (4)	Supplier	Film coat		(b) (4)
(b) (4)				
Total	NA	NA	(b) (4)	100.0

Abbreviations: NA, not applicable; USP, United States Pharmacopeia; NF, National Formulary

(b) (4)

(b) (4)

Component Name	Quality Standard	Function	Quantity per Unit (mg)	% w/w
(b) (4)				
Lesinurad	In-house	Active ingredient	200.00	(b) (4)
Allopurinol[3]	USP	Active ingredient	200.00	
Lactose Monohydrate	NF		(b) (4)	
Microcrystalline Cellulose	NF			
Crospovidone	NF			
Hydroxypropyl Cellulose	NF			
(b) (4)				(b) (4)
Film Coating				
Opadry Orange (b) (4)	Supplier	Film coat		(b) (4)
(b) (4)				
Total	NA	NA	(b) (4)	100.0

Abbreviations: NA, not applicable; USP, United States Pharmacopeia; NF, National Formulary

(b) (4)

(b) (4)

The Applicant relies for the approval of the proposed lesinurad/allopurinol FDC tablets [200mg/200mg; and 200mg/300mg; NDA 209203 is a 505(b)(2) submission] on FDA's previous finding of safety and efficacy for the reference drug Zurampic® (Lesinurad IR tablets,

[3] Global Submit – N209203 - 0010(11) dated 04/06/2017. Module 3.2.P.1. Description and Composition of the Drug Product. (Accessed on July 07, 2017)

[4] Global Submit – N209203 - 0010(11) dated 04/06/2017. Module 3.2.P.3.3. Description of Manufacturing Process and Process Controls. (Accessed on July 07, 2017)

200mg) and Zyloprim® (Allopurinol IR tablets, 100mg and 300mg).[5] To support the bridge from the single agent to FDC tablet, a phase 1, randomized, open-label, crossover study (# RDEA594-501) is conducted on both strengths to assess the relative bioavailability (BA) of the proposed lesinurad/allopurinol FDC tablets (200mg/200mg: Lot # AAAD; and 200mg/300mg: Lot # SAAD)] and coadministered lesinurad [Zurampic (lesinurad) tablets, 200mg: Lot # MPAD] and allopurinol tablets [Zyloprim (allopurinol) tablets, 100mg × 2: Lot # A99136, and 300mg: Lot # AC9309] in healthy adult subjects in fasted state.[5,6] This study also evaluated the effect of food on the pharmacokinetics (PK) of lesinurad/allopurinol 200/300 FDC tablets in healthy adult subjects. The review of the above study is under the purview of Division of Clinical Pharmacology 2 (DCP2), Office of Clinical Pharmacology (OCP). The OCP recommended approval of the lesinurad/allopurinol fixed dose combination product.[7]

Based on Applicant's analysis, the relative BA study results indicated that the higher strength (Lesinuard/allopurinol - 200mg/300mg) of the proposed FDC tablet is bioequivalent (BE) to that of coadministered lesinurad and allopurinol at the same dose levels since 90% confidence interval (CI) for geometric least squares mean ratios of test vs reference for all PK parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) for lesinurad, allopurinol, and active metabolite oxypurinol met BE criterion of 0.8-1.25 (Table A1 of Appendix).[6] For the lower strength (Lesinuard/allopurinol - 200mg/200mg), the same as above could be concluded except for C_{max} of Allopurinol [90% CI of (1.0905 – 1.2817)] which is outside the BE limit with respect to the upper bound (Table A1 of Appendix). According to the Applicant, this is not considered to be clinically relevant for either safety or efficacy based on the following:[8]

1. The pharmacodynamics (PD) effect of allopurinol component of the FDC should be unchanged because a high proportion of xanthine oxidase inhibition with allopurinol over any 24-hour period is due to oxypurinol as a result of its activity and longer elimination half-life compared to allopurinol.

2. Allopurinol AUC is more relevant PK marker for PD performance than C_{max} based on study RDEQ3170-206 [300mg(bid) vs 600mg(qd) provided comparable allopurinol AUC but twice Cmax for 600mg qd compared to 300mg bid].

3. The small increase in allopurinol C_{max} for the FDC relative to coadministered single agent for 200mg dose is not expected to change the safety profile of the product since the primary adverse reactions of skin rash and hypersensitivity are associated with higher oxypurinol exposures and the FDC tablet demonstrated BE to monoproducts with respect to oxypurinol.

[5] Global Submit – N209203 - 0000(1) dated 10/20/2016. Module 1.2. Cover Letters – Lesinurad/Allopurinol FDC Original NDA. (Accessed on July 07, 2017)
[6] Global Submit – N209203 - 0000(1) dated 10/20/2016. Module 5.3.1.1. RDEA594-501 - Synopsis. (Accessed on July 07, 2017)
[7] DARRTS – N209203 – REV-CLINPHARM-21(Primary Review) by SINGH, RENU dated 07/15/2017. (Accessed on July 18, 2017)
[8] Global Submit – N209203 – 0000(1) dated 10/20/2016. Module 2.7.1. Summary of Biopharmaceutics Studies and Associated Analytical Methods. (Accessed on July 07, 2017)

Based on discussion with the OCP reviewer, the observed small increase in allopurinol C_{max} for the lower strength of the FDC product is considered not clinically meaningful.

In addition to the relative BA study RDEA-594-501, the lesinurad/allopurinol FDC clinical development program also comprised of ALLO-101 study – an in vitro in vivo relationship to assess the impact of the in vitro dissolution profile of allopurinol on the PK parameters used to establish bioequivalence.[8,9] The primary objective was to determine whether defined and limited changes in in vitro dissolution impact of the in vivo PK and relative BA of allopurinol and the active metabolite oxypurinol and was intended to inform formulation development of the FDC tablet. (b) (4)

However, all of the formulations (Regiment B, C, and D) met BE criteria for oxypurinol (active metabolite of allopurinol) for C_{max} and AUC when compared to reference Zyloprim® (Regimen A) suggesting that despite the difference in PK performance of allopurinol among the various formulations, plasma exposures of oxypurinol were unchanged, thus the pharmacological effects from oxypurinol were likely unaffected. The Applicant, however, did not submit information on the qualitative and quantitative composition and dissolution data of the studied information. Since, the study was performed on a single agent allopurinol tablet and was intended to inform FDC formulation development, its relevance for quality control of the proposed FDC product or clinical relevance of the proposed dissolution method for FDC product may be absent from biopharmaceutics perspective. Further information with regards to this study was not requested.

The FDC formulation used in pivotal relative BA study differs from that of the proposed commercial formulation with respect to non-functional film coating material. Specifically, opadry (b) (4) based coating was used for formulation used in vivo study (RDEA594-501). (b) (4)

he non-functional coating was changed from (b) (4) based to (b) (4) (b) (4) based for commercial manufacturing that (b) (4) .[10,11] This change in non-functional

[9] Global Submit – N209203 – 0000(1) dated 10/20/2016. Module 5.3.3.1. ALLO-101-Synopsis. (Accessed on July 11, 2017)

[10] Global Submit – N209203 – 0004(5) dated 02/02/2017. Module 3.2.P.2. Pharmaceutical Development – Drug Product. (Accessed on July 07, 2017)

[11] Global Submit – N209203 – 0000(1) dated 10/20/2016. Module 3.2.P.5.4. Control of Drug Product – Batch Analyses. (Accessed on July 07, 2017)

film coating is bridged by batch release, stability and comparative dissolution profile data as agreed upon in IND type C meeting.[2] The dissolution data supporting the bridging of pivotal relative BA and commercial formulation is reviewed under the section "**Bridging of Formulations**". Table A2 of Appendix provides information on drug product lots (lots used in in vivo relative BA study, registration stability, supporting registration stability, GMP lots) manufactured at AstraZeneca AB, use of these drug product lots, and drug substance lots used for drug product manufacturing.

The biopharmaceutics review focuses on the review of the following:

1. Dissolution method development report for the proposed FDC tablets (i.e., method development including discriminating ability of the method),

2. Physiologically based pharmacokinetic (PBPK) modeling and simulation in support of the proposed particle size distribution (PSD) of both drug substances (Lesinurad and Allopurinol), and wider dissolution acceptance criterion for lesinurad (Q (b)(4)% in 45 min). In addition, review of PBPK modeling and simulation exercise in support of dissolution acceptance criterion for allopurinol Q (b)(4)% in 30 min (however, proposed criterion is Q= (b)(4)% in 20 min) and prediction of in vivo perf mance of the lower strength of FDC tablet in comparison to that of the higher strength is also performed,

3. In vitro dissolution based bridging in support of the change in non-functional film coat [pivotal relative BA formulation (b)(4) based coating) vs intended commercial formulation (b)(4) based coating)],

4. Review of the Applicant's responses to two biopharmaceutics requests dated January 03, 2017,[12] and March 15, 2017 (Table A3 and A4 of Appendix respectively),[13] and responses on PBPK model questions received/discussed during teleconference with the Applicant on July 06, 2017 (Table A5 of Appendix).

Review Summary

The proposed dissolution method, discriminating ability of the method, dissolution acceptance criterion, dissolution analytical method, PBPK modeling and simulation in support of the proposed PSD of both drugs and wider dissolution acceptance criterion of lesinurad, in vitro bridging for change in non-functional film coating for the proposed FDC IR tablet is reviewed in detail and found adequate. The Applicant adequately responded to the two biopharmaceutics information requests and PBPK questions discussed during the teleconference on July 06, 2017 during the review cycle. The dissolution method and acceptance criterion are detailed in Table 2 below. *It should be noted that though the proposed PBPK model is adequate for supporting PSD*

[12] Global Submit – N209203 – 0004(5) dated 02/02/2017. Module 1.2. Response to Information Request Dated 03 Jan 2017. (Accessed on July 07, 2017)

[13] Global Submit – N209203 – 0008(9) dated 03/28/2017. Module 1.2. Response to CMC/Biopharm Information Request Dated 15 Mar 2017. (Accessed on July 07, 2017)

of drugs and wider dissolution acceptance criterion for lesinurad, the same model would require further refinement (e.g., challenging the model with non-BE FDC batch) for defining the dissolution safe space and broadening its application for lifecycle management of the proposed FDC IR tablets (e.g., supporting biowaiver for major manufacturing/formulation changes). This will be provided to the Applicant in a General Advice Letter (Refer Table A6 of Appendix).

Table 2. Dissolution Method and Acceptance Criterion for the Proposed Lesinurad and Allopurinol FDC IR Oral Tablets (200mg/200mg; and 200mg/300mg) for Finished Product Batch Release and Stability

Method Source	USP Apparatus	Rotation Speed	Dissolution Medium	Medium Volume	Medium Sampling Volume	Medium Temperature	Acceptance Criterion(a)	
In house	2 (Paddle)	75 rpm	0.01N HCl with 1% sodium lauryl sulfate (SLS)	900mL	1mL[a,b]	37°C ± 0.5°C	Lesinurad	Q (b) (4)% in 45min[c]
							Allopurinol	Q= (b) (4) 20min[d]

[a] Dissolution sample clarified by (b) (4)

[b] Analyzed using HPLC/UV analytical method

[c] Based on in silico physiologically based pharmacokinetic (PBPK) modeling and simulation (Note that in vitro dissolution of primary/supporting registration batches and in vivo relative BA study batch supports Q = (b) (4)% in 30 min for lesinurad. However, Q = (b) (4)% in 45 min was studied by PBPK modeling and simulation and no in vivo impact of this wider dissolution specification for sinurad was observed and hence is proposed by the Applicant and is adequate)

[d] Based on submitted in vitro dissolution data of primary/supporting registration batches and in vivo relative BA study batch (Note that Q = (b) (4)% in 30 min for allopurinol was studied by PBPK modeling and simulation and no in vivo impact of this wider dissolution specification for allopurinol was observed; however, tighter dissolution acceptance criterion is proposed for allopurinol by the Applicant which is adequate)

Dissolution Risk/Mitigation Assessment (based on Biopharmaceutics Review): Low, the Applicant has included dissolution testing for quality control (finished product batch release and stability) of the proposed FDC product. The proposed wider dissolution acceptance criterion for Lesinurad (Q = (b) (4)% in 45min) based on PBPK model not challenged by non-BE batch is acceptable. This because, dissolution acceptance criterion of allopurinol (Q = (b) (4)% in 20 min) is tighter and is proposed based on submitted in vitro data of in vivo relative BA and registration batches which would minimize the risk if any with respect to the wider dissolution acceptance criterion for lesinurad. Additionally, the above is also supported by other reasons and observations discussed in detail in the review "Justification of the Dissolution Specification Limits for Lesinurad and Allopurinol". Further, the particle size of lesinurad and allopurinol are controlled and proposed specifications are supported by PBPK. Overall, because of appropriate control strategy, the risk related to failure of dissolution is mitigated.

ONDP-Division of Biopharmaceutics reviewed NDA 209203 and responses to biopharmaceutics information requests. The NDA 209203 is recommended for Approval from a Biopharmaceutics perspective. A general advice letter will be sent to the Applicant with regards to the possible refinement of the proposed PBPK model for its potential application in support of major post-approval CMC changes and lifecycle management of the proposed drug product (Refer Table A6 of Appendix for the General Advice Letter).

Table 3. List of Submissions Reviewed

SEQUENCE #	SUBMISSION(S) DATE	MODULE #	SUBMISSION DOCUMENT(S) REVIEWED
		1.2.	Cover Letters – Lesinurad/Allopurinol FDC Original NDA
0000(1)	10/20/2016	1.6.3.	Correspondence Regarding Meetings - Type-C Meeting Minutes 19 Jan 2016
		2.3.P.	Drug Product
		2.7.1.	Summary of Biopharmaceutics Studies and Associated Analytical Methods.
		3.2.P.5.1.	Specifications 200mg/200mg Tablets
		3.2.P.5.1.	Specifications 200mg/300mg Tablets
		3.2.P.5.4.	Control of Drug Product – Batch Analyses.
		3.2.P.5.6.	Justification of Specifications
		3.2.P.8.1.	Stability Summary and Conclusion
		5.3.1.1.	RDEA594-501 - Synopsis
		5.3.1.3.	Solubility of Lesinurad (RDEA594) Drug Substance (AR-594-066-3.0).
		5.3.3.1.	ALLO-101-Synopsis
		5.3.1.3.	SR16-019 - Lesinurad FDC PBPK Modeling and Simulations
0004(5)	02/02/2017	1.2.	Response to Information Request Dated 03 Jan 2017.
		3.2.P.2.	Pharmaceutical Development – Drug Product
			Pharmaceutical Development – Dissolution Method (AR-594-FDCA-004-2.0) - Appendix A
			Pharmaceutical Development – Dissolution Method (AR-594-FDCA-024) - Appendix B
		3.2.P.5.2.	Analytical Procedure for Lesinurad and Allopurinol Dissolution
		3.2.P.5.3.	Validation of Analytical Procedure for Dissolution
0008(9)	03/28/2017	1.2.	Response to CMC/Biopharm Information Request Dated 15 Mar 2017
0010(11)	04/06/2017	3.2.P.1.	Description and Composition of the Drug Product
		3.2.P.2.	Manufacturing Process Development
		3.2.P.3.2.	Batch Formula
		3.2.P.3.3.	Description of Manufacturing Process and Process Controls

Concise Description Outstanding Issues Remaining: No pending issues

Biopharmaceutics Classification System (BCS) Designation

According to the Applicant, lesinurad is a BCS class 2 drug substance and allopurinol is a BCS class 4 drug substance.[14,15]

Solubility:

Lesinurad: Based on Table 4, lesinurad exhibits pH dependent solubility with dose/solubility ratio of > 250mL at pH less than or equal to 5 and < 250mL at pH greater than or equal to 6 considering 200mg strength and hence fits the BCS definition[16] of low solubility. However, lesinurad is a low biopharmaceutical risk compound as it exhibits high solubility in intestinal pH media and dose linearity across the range of 100mg to 1200mg.[15]

Allopurinol: Based on Table 5, allopurinol exhibits pH independent solubility with dose/solubility ratio of > 250mL across gastrointestinal pH range considering the highest strength (300mg; i.e., 300mg/0.78mg/mL ~ 385mL). Hence, allopurinol is a low solubility compound according to the BCS definition[16]. The highest dosage strength of allopurinol to be considered highly soluble by BCS classification is approximately 200 mg.

Table 4. Lesinurad (b) (4) Aqueous Solubility in Different Media at 37°C[17]

Media	Final pH	Solubility (mg/mL)
FaSSIF pH 6.5	5.6	3.2
FeSSIF pH 5.0	5.0	1.7
SGF pH 1.6 (HCl 30 mM, I = 0.1 M)	1.5	0.0061
pH 4 buffer (Citrate 25 mM, I = 0.1 M)	4.0	0.045
pH 5 buffer (Acetate 25 mM, I = 0.1 M)	5.1	0.60
pH 6 buffer (Citrate 22 mM, I = 0.1 M)	5.9	5.2
pH 6.5 buffer (Phosphate 25 mM) + NaOH	6.0	17
pH 6 buffer (Citrate 22 mM) + NaOH	5.9	43
FaSSIF pH 6.5 + NaOH	5.9	21
0.01 N HCl with 1.0% SLS	2.30	1.33

Data from AR-594-FDCA-004 and AR-594-FDCA-005
Abbreviations: FaSSIF, Fasted-State Simulated Intestinal Fluid; FeSSIF, Fed-State Simulated Intestinal Fluid; SGF, Simulated Gastric Fluid; SLS, sodium lauryl sulfate.

[14] Global Submit – N209203 – 0000(1) dated 10/20/2016. Module 5.3.1.3. Solubility of Lesinurad (RDEA594) Drug Substance (AR-594-066-3.0). (Accessed on July 08, 2017)
[15] Global Submit – N209203 – 0004(5) dated 02/02/2017. Module 3.2.P.2. Pharmaceutical Development – Drug Product. (Accessed on July 08, 2017)
[16] FDA Draft Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate -Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. May 2015. (Accessed on July 08, 2017)
[17] Global Submit – N209203 – 0000(1) dated 10/20/2016. Module 5.3.1.3. SR16-019 - Lesinurad FDC PBPK Modeling and Simulations. (Accessed on July 08, 2017)

Table 5. Allopurinol Aqueous Solubility in Different Media at 37°C

Media	Solubility (mg/mL)
0.1 N HCl	0.91
0.01 N HCl	**0.85**
pH 4.5 Acetate Buffer (50 mM)	0.78
pH 6.8 Phosphate Buffer (50 mM)	0.79
0.01N HCl with 1.0% SLS	0.87

Data from AR-594-FDCA-004.
Abbreviations: HCl, hydrogen chloride; SLS, sodium lauryl sulfate.

Permeability:

Lesinurad: Based on prescribing information or drug labeling of Zurampic® (Lesinurad IR tablets, 200mg), the absolute bioavailability of lesinurad is approximately 100% which supports its high permeability.[18,19] The Caco-2 permeability report for lesinurad under NDA 207988 and cross-referenced in this 505(b)(2) NDA is also supportive of high permeability of lesinurad.[20]

Allopurinol: Based on Caco-2 permeability assay, allopurinol demonstrated a passive permeation mechanism and concentration independent permeation, and is not an efflux substrate. The permeability (Papp) of allopurinol was slightly lower than the high permeability marker minoxidil (Allopurinol at 100 µmol/L: 4.49 x 10^{-6} ± 1.04 10^{-6} cm/s; Minoxidil at 10 µmol/L: 5.45 10^{-6} ± 1.04 10^{-6} cm/s) which is indicative of low permeability characteristics of allopurinol.[21] The Applicant states that "allopurinol falls just short of the BCS definition for both highly soluble and highly permeable."[15]

Dissolution:[22]

The Applicant studied multimedia dissolution (USP II, 75rpm) for both lower (200mg/200mg, Lot # AAAD used in pivotal relative BA study) and higher (200mg/300mg, Lot # SAAD used in pivotal relative BA study) strength in BCS media [0.1N HCl (pH 1.1), 50mM acetate buffer (pH 4.5), and 50mM potassium phosphate buffer (pH 6.8)]. Figures 1 and 2 represent these dissolution profiles for lesinurad and allopurinol respectively. In all three media, the dissolution

[18] Full Prescribing Information – Zurampic® (Accessed on July 08, 2017)
[19] Global Submit – N209203 – 0000(1) dated 10/20/2016. Module 5.3.1.3. rdea594-131 - RDEA594-131 - A Study to Assess the Absolute Bioavailability of a Single Oral Dose of Lesinurad with Respect to an Intravenous Micro Tracer Dose of [14C] Lesinurad in Healthy Male Subjects - STF. (Accessed on July 08, 2017)
[20] Global Submit – N209203 – 0000(1) dated 10/20/2016. Module 4.2.2.2. 8ARDEP3R1 - Caco2 Permeability Assay - STF. (Accessed on July 08, 2017)
[21] Global Submit – N209203 – 0000(1) dated 10/20/2016. Module 4.2.2.3. SR16-014 - Invitro Permeability Report - BS001265-38. (Accessed on July 08, 2017)
[22] Global Submit – N209203 – 0004(5) dated 02/02/2017. Module3.2.P.2. Pharmaceutical Development Report - Dissolution Method (AR-594-FDCA-004-2.0) - Appendix A. (Accessed on July 09, 2017)

profiles were equivalent for both FDC tablet strengths, Lots SAAD and AAAD, manufactured using the same lots of both active substances. Lesinurad do not meet rapid dissolution definition (incomplete dissolution in pH 1.1 and 4.5); whereas, for Allopurinol, lot SAAD do meet very rapid dissolution definition (<85% dissolution in 15min). However, these multimedia dissolution data is not relevant from BCS perspective since lesinurad and allopurinol are BCS class 2 and 4 drugs respectively (b) (4) .

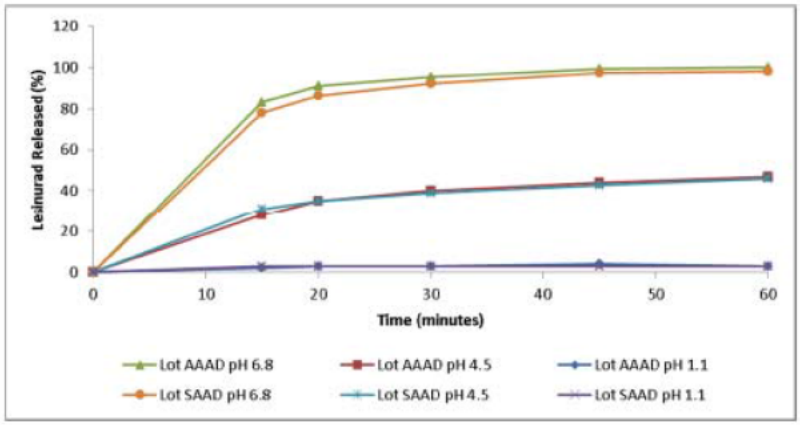


Figure 1. Mean Dissolution (USP II, 7/5 rpm) of Lesinurad From FDC Tablets, 200/200 Lot AAAD and 200/300 Lot SAAD, in BCS Dissolution Media (n=12)

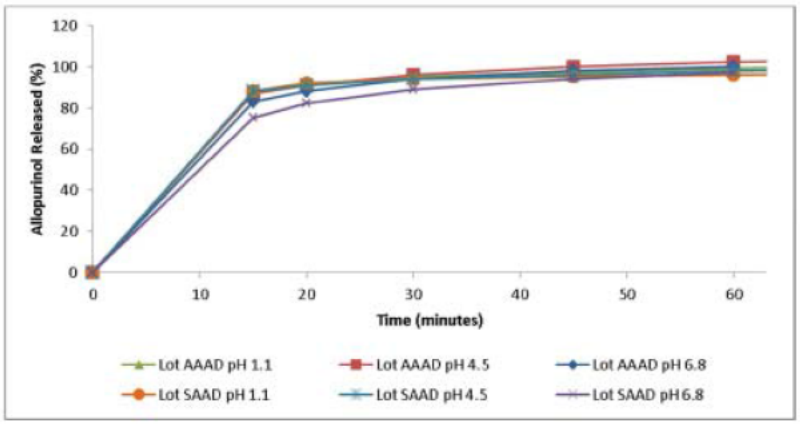


Figure 2. Mean Dissolution (USP II, 75 rpm) of Allopurinol From FDC Tablets, 200/200 Lot AAAD and 200/300 Lot SAAD, in BCS Different Dissolution Media (n=12)

Reviewer's Assessment:

A request for BCS designation of the product is not made. The information provided by the Applicant on solubility and permeability of lesinurad and allopurinol supports BCS 2 and 4

classifications of these drug substances respectively. Further, the Applicant has conducted in vivo relative BA study (RDEA594-501) on both strengths of the proposed product (b) (4) However, the information that lesinurad is BCS 2 and allopurinol is BCS 4 drugs may be helpful in making other review decisions (e.g., in vitro dissolution acceptance criterion, risk assessment, and lifecycle management considerations).

***Dissolution Method and Acceptance Criteria*[22]**

Dissolution Method:[22]

Table 6 presents the information on the proposed dissolution method and acceptance criterion for the proposed lesinurad and allopurinol FDC IR oral tablets (200mg/200mg, and 200mg/300mg). Dissolution method development was conducted using opadry (b) (4) based film coated tablets. Since, no impact of change in non-functional film coat from opadry (b) (4) to opadry (b) (4) is observed (Refer "Bridging of Formulations" for details), the dissolution method development efforts using (b) (4) based film coated tablets including tablets used in in vivo relative BA study (Lot # AAAD and SAAD) is reasonable. Table 7 presents information on FDC tablet batches used in dissolution method development.

Table 6. Proposed Dissolution Method and Acceptance Criterion for the Proposed Lesinurad and Allopurinol FDC IR Oral Tablets (200mg/200mg; and 200mg/300mg) for Finished Product Batch Release and Stability

Method Source	USP Apparatus	Rotation Speed	Dissolution Medium	Medium Volume	Medium Sampling Volume	Medium Temperature	Proposed Acceptance Criterion(a)	
In house	2 (Paddle)	75 rpm	0.01N HCl with 1% sodium lauryl sulfate (SLS)	900mL	1mL[a,b]	37°C ± 0.5°C	Lesinurad	Q (b) (4)% in 45min[c]
							Allopurinol	Q (b) (4)% in 20min[d]

[a] Dissolution sample clarified by (b) (4)

[b] Analyzed using HPLC/UV analytical method

[c] Based on in silico physiologically based pharmacokinetic (PBPK) modeling and simulation (Note that in vitro dissolution of primary/supporting registration batches and in vivo relative BA study batch supports Q = (b) (4)% in 30 min for lesinurad. However, Q (b) (4) in 45 min was studied by PBPK modeling and simulation and no in vivo impact of this wider dissolution specification for lesinurad was observed and hence is proposed by the Applicant)

[d] Based on submitted in vitro dissolution data of primary/supporting registration batches and in vivo relative BA study batch (Note that Q = (b) (4)% in 30 min for allopurinol was studied by PBPK modeling and simulation and no in vivo impact of this wider dissolution specification for allopurinol was observed; however, tighter dissolution acceptance criterion is proposed for allopurinol by the Applicant)

Table 7. Lesinurad/Allopurinol Fixed Dose Combination Tablet Batches Used in Dissolution Method Development

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System Suitability Criteria for both drugs

System Suitability Test	Acceptance Criteria
Interference	Confirm that the blank (diluent) injection has no interference at the retention time of the lesinurad and allopurinol peaks
Injection Repeatability	Confirm the % RSD of 5 injections of the standard is not greater than (b) (4) for the lesinurad and allopurinol peak
Tailing Factor	Confirm the lesinurad and allopurinol peaks in an injection of standard have a tailing factor of not less than (b) (4) and not more than (b) (4)

Abbreviation: RSD, relative standard deviation

Dissolution Acceptance Criterion:

The Applicant proposed the dissolution acceptance criterion of Q = (b) (4)% in 45 min and Q = (b) (4)% in 20 min for lesinurad and allopurinol for both finished batch release and stability of the proposed FDC IR tablets (200mg/200mg; and 200mg/300mg) tested using the proposed dissolution method (Table 6).[25,26,27] The Applicant proposed the above dissolution acceptance criterion based on the following:[28]

(b) (4)

[redacted]

[25] Global Submit – N209203 – 0000(1) dated 10/20/2016. Module 3.2.P.5.1. Specifications 200mg/200mg Tablets. (Accessed on July 10, 2017)
[26] Global Submit – N209203 – 0000(1) dated 10/20/2016. Module 3.2.P.5.1. Specifications 200mg/300mg Tablets. (Accessed on July 10, 2017)
[27] Global Submit – N209203 – 0000(1) dated 10/20/2016. Module 3.2.P.8.3. Stability Data. (Accessed on July 10, 2017)
[28] Global Submit – N209203 – 0000(1) dated 10/20/2016. Module 3.2.P.5.6. Justification of Specifications. (Accessed on July 10, 2017)

(b) (4)

Based on the review of the mean and individual in vitro dissolution data for all primary/supporting registration and GMP batches (including in vivo relative BA study lot SAAD and AAAD of higher and lower strength respectively; Table A2 of Appendix) of both strengths of the proposed FDC product generated using the proposed dissolution method supports acceptance criterion of Q = (b) (4) for lesinurad and Q = (b) (4) in 20 min for allopurinol respectively (Based on USP <711> stage 2 criteria; Figures 8 and 9). However, the acceptance criterion of Q = (b) (4)% in 45 min for lesinurad is acceptable due to the absence of in vivo impact as evaluated by validated PBPK model (Refer section ""Physiologically Based Pharmacokinetic Model for Lesinurad/Allopurinol FDC Tablets"). The individual (n=12) and mean dissolution

data along with variability (%RSD) for primary registration batches (Appendix G of the cited reference[22]) and supporting registration batches and GMP lots[29] of both strengths can be accessed at the respective cited references. It is noted that one FDC tablet of batch SAAF (supporting registration batch of higher strength) provided lesinurad dissolution of 79% in 30 min; however, lesinurad dissolution variability (%RSD) at this time point is only 3.6%. The maximum observed variability (%RSD) in dissolution using the proposed method is 9.2% for lesinurad and 6.3% for allopurinol across all tested batches and time points. The above mentioned dissolution variability for both drugs was observed for earlier time point of 15min.

As shown in Table 13, 14, and 15, strength dependent dissolution is not observed for both drugs and all exhibit batches demonstrate dissolution similarity for both drugs. Hence, the same dissolution acceptance criterion of lesinurad and allopurinol for both strengths is supported. It should be noted that the in vivo relative BA study batches AAAD (200mg/200mg) and SAAD (200mg/300mg) provided the slowest drug release rate for both allopurinol and lesinurad relative to other registration batches (Figure 8). This was attributed by the Applicant to slightly larger particle size distribution of (b) (4) for these in vivo batches compared to other registration batches. However, dissolution profiles of these in vivo batches and other registration batches are similar for both drugs (Table 13, 14, and 15).

Figure 8. Dissolution of Lesinurad (Left) and Allopurinol (Right) From Primary Registration Lots of FDC Tablets (200mg/200mg – AAAB, AAAC, AAAD; 200mg/300mg – SAAB, SAAC, SAAD) Using the Proposed Quality Control (QC) Method

[29] Global Submit – N209203 – 0004(5) dated 02/02/2017. Module 3.2.P.2. Dissolution Method (AR-594-FDCA-024) - Appendix B. (Accessed on July 10, 2017)

Figure 9. Dissolution of Lesinurad (Left) and Allopurinol (Right) From Supporting Registration and GMP Lots of FDC Tablets (200mg/200mg – AAAE, AAAF, AAAG, PAAB; 200mg/300mg – SAAF, SAAG, SAAH, RAAB) Using the Proposed Quality Control (QC) Method

Table 13. Summary of Lesinurad and Allopurinol *f2* Values for Primary Registration Batches Relative to the Higher Strength Bioequivalence Batch, Lot SAAD (Calculated by the Applicant)

Batch	Strength	Lesinurad f2*	Allopurinol f2*
AAAB	200/200	57	56
AAAC		57	67
AAAD		69	77
SAAB	200/300	63	68
SAAC		57	74
SAAD		Reference	Reference

*Lesinurad and allopurinol f2 values calculated using 15, 20, and 30 minute timepoints. Allopurinol f2 values included for reference, although the percent dissolved values for all batches were >85% by the second timepoint (20 minutes).

Table 14. Summary of Lesinurad and Allopurinol *f2* Values for Supporting Registration and GMP Batches Relative to the Higher Strength Bioequivalence Batch, Lot SAAD (Calculated by the Reviewer)

Batch	Strength	Lesinurad *f2**	Allopurinol *f2*
AAAE	200mg/200mg	81.17	*f2* calculation is not necessary since dissolution for all batches was >85% in 15 min indicating similar dissolution as that of the reference. Batch SAAF provided dissolution of 82% in 15 min and 88% in 20 min. According to this reviewer, since SAAF is not significantly slower than the reference batch, dissolution profiles can be considered similar.
AAAF		81.17	
AAAG		62.72	
PAAB		64.63	
SAAF	200mg/300mg	65.96	
SAAG		89.35	
SAAH		77.88	
RAAB		55.73	
SAAD		Reference	Reference
* *f2* calculated considering time points up to 30 min			

Table 15. Summary of Lesinurad and Allopurinol *f2* Values for Primary/Supporting Registration and GMP Batches of the Lower Strength Relative to the Lower Strength Bioequivalence Batch, Lot AAAD (Calculated by the Reviewer)

Batch	Strength	Lesinurad *f2**	Allopurinol *f2*
AAAB	200mg/200mg	47.29	*f2* calculation is not necessary since dissolution for all batches was >85% in 15 min indicating similar dissolution across batches. However, reference batch AAAD provided dissolution of 82% in 15 min and 89% in 20 min. According to this reviewer, since AAAD is not significantly slower than the reference batch, dissolution profiles can be considered similar. Further, AAAD is also studied in vivo which is considered to be BE to the coadministered single agent tablets**
AAAC		47.29	
AAAE		60.04	
AAAF		61.19	
AAAG		51.18	
PAAB		52.24	
AAAD		Reference	Reference

* *f2* calculated considering time points up to 30 min
** It should be noted that batch AAAD failed w r.t to 90% CI BE upper limit (observed 1.28) of Cmax of Allopurinol. However, this is considered not meaningful as discussed previously.

It is important to note that the proposed dissolution acceptance criterion of Q = (b) (4)% in 20min for allopurinol rejects the drug product batch manufactured with larger particle size of allopurinol (i.e., larger than the proposed particle size; (b) (4) allopurinol; product lot A10297-13; Figure 6; Table 16) of which in vivo impact is not known. Further, Q = (b) (4)% in 20 min for allopurinol also rejects (b) (4) drug product batch of which in vivo impact is not known (product lot A10257-161; Figure 7; Table 11 and 15). Though, lesinuard proposed acceptance criterion of Q = (b) (4)% in 45 min does not reject (b) (4) batch (% dissolved at 30 min and 45 min is (b) (4)% respectively), it rejects the (b) (4) batch that represents process change based on *f2* of 44 (A10257-161 vs SAAD). Considering Q = (b) (4)% in 45min for lesinurad is supported based on validated PBPK model (discussed later) and Q = (b) (4)% in 20 min for allopurinol will reject the FDC product that is (b) (4), the proposed criterion of Q = (b) (4)% in 45 min for lesinurad is acceptable. Though Q = (b) (4) is evaluated by PBPK model and showed absence of the impact of the slower dissolution profile, considering that (b) (4) batch of which in vivo impact is not known (not studied by PBPK model) and Q = (b) (4)% in 20 min criterion for allopurinol rejects this batch, the criterion of Q = (b) (4)% in 20 min is adequate since Q = (b) (4) does not reject this batch (% dissolved in (b) (4) min = (b) (4)%; mean of n=12). Further, the PBPK model that supported Q = (b) (4)% in 45min and Q = (b) (4)% in (b) (4) (b) (4) for allopurinol is not challenged by non-BE batch to define dissolution safe space limit. ***Considering all of the above factors, wider dissolution acceptance criterion of Q = (b) (4)% in 45 min for lesinurad and stringent dissolution acceptance criterion of Q = (b) (4)% in 20 min for allopurinol of the proposed FDC product is acceptable.***

Table 16. Evaluation of Appropriateness of the Proposed Dissolution Acceptance Criterion of Q (b)(4)% in 20 min for Allopurinol

Test Product	Reference Product	*f2*	*% Dissolved at 20 min for Test*
Product lot A10297-13 (200mg/300mg) (b)(4) Allopurinol D(v,0.1) = (b)(4) m, D(v,0.5) = µm, D(v,0.9) = µm	Product lot SAAD (200mg/300mg) (b)(4) Allopurinol D(v,0.1) = (b)(4) m, D(v,0.5) = m, D(v,0.9) = µm	44	78 (mean of n=6)
Product lot A10297-13 (b)(4) batch	Product lot SAAD Representative of intended manufacturing	40	76 (mean of n=12)
Proposed particle size distribution of allopurinol - D(v,0.5) = NMT (b)(4) µm; D(v,0.9) = NMT (b)(4) µm			

Dissolution Trend in Stability:[27]

The Applicant has collected dissolution profile (15min, 20min, 30min, 45min, and 60min) for all primary/supporting registration batches (N=14, 7 batches of each strength) stored at long term (25°C/60% RH), intermediate (30 °C/75% RH), and accelerated (40°C/75%RH) stability conditions. An increasing or decreasing trend in dissolution is not observed for any of the batches in stability and all stability batches meet the proposed dissolution acceptance criterion for both drugs at all of the above stability conditions.

Reviewer's Assessment: ***Adequate***

Dissolution Method: The Applicant proposed in house dissolution method (USP 2, 75 rpm, 900mL of 0.01N HCl containing 1% SLS) for finished product batch release and stability testing of both strengths of the proposed lesinurad and allopurinol IR oral tablets. The proposed method is adequate based on the availability of sufficient sink condition for dissolution of both drugs, demonstration of suitability of the proposed paddle speed, discriminating ability of the proposed dissolution method towards critical material attributes (allopurinol particle size) and critical process parameters (b)(4) batch).

Dissolution Analytical Method: The proposed gradient-RP-HPLC-UV analytical method for analysis of lesinurad and allopurinol dissolution samples of the proposed FDC IR tablets is adequately validated.

Dissolution Acceptance Criterion: The proposed dissolution acceptance criterion of Q = (b)(4)% in 45 min and Q = (b)(4)% in 20 min supported based on (1) in vitro dissolution data generated using

the proposed dissolution method, (2) discriminating ability of the proposed dissolution acceptance criterion towards critical material attributes (allopurinol particle size) and critical process parameters (b) (4) batch), and (3) the absence of in vivo impact of the wider lesinurad dissolution acceptance criterion based on validated PBPK model is adequate and acceptable for both finished product batch release and stability of both strengths of the proposed FDC IR tablets. (Note that PBPK model supporting wider dissolution acceptance criterion is discussed below in detail)

Physiologically Based Pharmacokinetic (PBPK) Model for Lesinurad/Allopurinol FDC Tablets[17]

Introduction:

Physiologically-based pharmacokinetic (PBPK) models were developed using GastroPlus™ software (Version 9.0, Simulation Plus Inc., Lancaster, CA) to describe the in vivo performance of lesinurad and allopurinol following administration of the FDC tablet to humans. The objective of this investigation was to utilize physiologically-based absorption modeling and simulation approach to:

1. Assess the in vivo performance of the FDC tablets and single agent tablets for bioequivalence evaluation
2. Support the proposed dissolution specifications for the FDC product (Specifically, support proposed wider dissolution specification for lesinurad for the proposed dissolution method. Simulations were conducted to evaluate the PK performance of FDC products tested in clinical Study 501 and of a virtual batch with dissolution of (b) (4)% at 45 minutes for lesinurad and at (b) (4) for allopurinol) (Note that through Q (b) (4)% in (b) (4) min was evaluated for allopurinol by PBPK, the proposed criterion is tighter: Q = (b) (4)% in 20 min)
3. Support lesinurad and allopurinol particle size distribution specifications for the FDC tablets
4. Assess dose proportionality for the 300 mg and 200 mg allopurinol strengths of the FDC tablet

PBPK model development was performed using formulation properties (e.g., in vitro dissolution data) and compartmental model PK parameters obtained from fitting of the compartmental PK model to clinically observed plasma drug concentration time profile of the FDC product that were tested in vivo relative BA study (RDEA-594-501). The FDC product used in the study 501 were coated with Opdary (b) (4) based film coating; whereas, the intended commercial formulation proposed has Opdary (b) (4) based film coating. As mentioned under the section

"Bridging of Formulations", the change in non-functional film coating is not expected to have in vivo impact since it is appropriately bridged by in vitro dissolution data and supported by additional reasons discussed. The modeling and simulation involved the following steps – model building, model validation, and model application which are discussed below. Figure 10 provides schematic followed for PBPK absorption model development, optimization, verification/validation, and application which was submitted in response to the biopharmaceutics information request # 1.[12] The details of PBPK model development, validation and application, and related results for each of these steps can be found at the cited reference.[17]

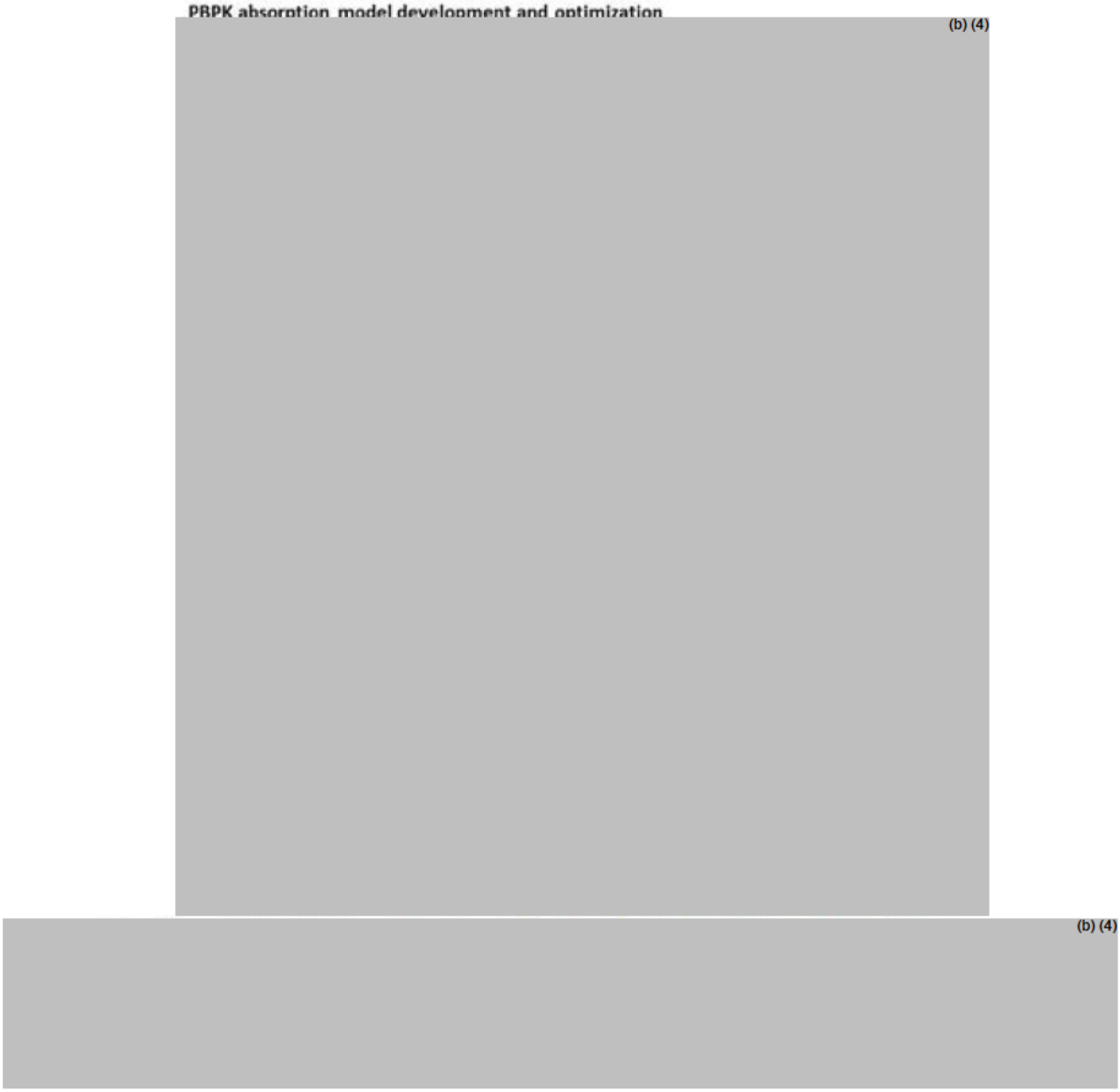

Figure 10. General Scheme for PBPK Absorption Model Development, Optimization, Verification, and Application

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Attachment – Final Risk Assessment

DP attribute/ CQA	Factors that can impact the CQA	O[1]	S[1, 2]	D[1]	FMECA RPN #	Comment & considerations
Appearance	• Quality of the formulation input materials • (b) (4) variability • (b) (4) process parameter variability • Tablet coating process parameter variability • Acceptance criteria for coating materials	2	1	2	4	• (b) (4) • • • • •
Identification	• incorrect drugs formulated • no drug formulated	1	3	1	3	• Probability of occurrence should be low and detectability high if applicant adheres to GMPs: specification for drug substances include specific (FTIR) identification testing, consistent with Q6A • Severity of failure would depend on situation (incorrect or no drug present)[2] • Final drug product specifications include two non-specific orthogonal tests for the drug identity confirmation (consistent with Q6A)
Assay, degradation products	• input purity of APIs • input purity of excipients • incorrect amounts of APIs formulated • impurity formation due to interaction of drugs with (b) (4)	3	3	2	18	• Total impurities allowed in input APIs limited by respective specifications • Inorganic impurities and residual solvents also tested for input APIs with acceptance criteria proposed • Note heavy metal testing of lesinurad API has been removed during development with justification to be considered; applicant claims no (b) (4) used in allopurinol synthesis and provide test data to justify absence of routine testing • Excipients are of compendial quality, i.e., suitable for solid oral

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability

[2] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

	• degradation of drug substances due to [redacted] (protection from environment) • presence of [redacted] • CU problems (*vide infra*)					• dosage forms [redacted] film coating prepared from compendial ingredients as well) • GMP adherence should prevent incorrect amounts of APIs formulated • Applicant has addressed API/excipient compatibility in P.2.1.2 (can also be gauged indirectly based on stability data provided in P.8) • Lesinurad [redacted]) only formed by forced [redacted]; [redacted] of lesinurad leads to [redacted], but subjecting drug substance to 70°C/75%RH for 1 month only leads to < [redacted]% of this [redacted] allopurinol related compounds [redacted] and [redacted] (USP) are degradants with limits of NMT [redacted]% w/w each in the drug product specifications • [redacted]
Physical stability (solid state of APIs, dosage form)	• polymorphic or pseudo-polymorphic [redacted]) conversion of drug substance	1	3	5	15	• Lesinurad is said to exist in two crystalline Forms 1 and 2 and an [redacted]; Form 2 is said to be the most [redacted]; Applicant claims to have performed "extensive crystal form screening" and mention only some irrelevant [redacted]; allopurinol is said to have "one known crystal form" but no references are provided in support of this statement and it is not clear that the FTIR identification test would be specific for the crystalline form • [redacted] applicant has also provided limited XRPD data for tablets stored for 6 months under refrigerated conditions and states that these data demonstrate the continued presence of form 2 (process team agreed with that assessment) • Note, FTIR (used for ID of drug substances) can distinguish the [redacted] (see S.1.3.5) of lesinurad • Applicant has not identified a [redacted], which is an important point considering the [redacted] and the very slight solubility of lesinurad in water (~100

						mcg/mL); lesinurad is not hygroscopic • Neither drug product specification includes a test for crystalline form for either drug substance
Uniformity of dosage units	• lack of (b) (4) (b) (4)	2	3	3	18	• (b) (4) • Content uniformity is tested as part of drug product specification as per USP <905>
Microbial limits	• microbial load of input materials for formulation • microbial contamination during processing (b) (4) • microbial growth during shelf life	1	3	5	15	• Applicant proposes to test one batch of drug product annually for microbial limits (periodic quality indicator test or PQIT) • Applicant claims (b) (4) of drug substances and the dosage form render these as non-viable for microbial growth (data provided for drug product in P.5.6.7 as per Q6A) • The applicant indicates that historical data show the drug product complies with the microbial limits testing requirements of the USP
Drug Release or Dissolution	• polymorph conversion of APIs • changes in input excipients • API particle size change • (b) (4) particle size • (b) (4) • tablet hardness	3	3	2	18	• Polymorph conversion is unlikely considering that the most (b) (4) of lesinurad is being formulated and other information presented above for the physical stability CQA; allopurinol is said to only have a single crystalline form • Excipients are of compendial grade and in common use for solid oral dosage forms • API particle size acceptance criteria examined relative to a parameter sensitivity analyses for dissolution (see P.2.7.1.3.5.1) • Applicant notes that (b) (4) particle size does impact dissolution (see report AR-594-FDCA-004-1.0, p. 41); see minor impact of (b) (4)) on dissolution in fig. 21 of P.2, Manufacturing Process Development • An increase in (b) (4) was observed at 12 months

						for 25 °C/60% RH and 30 °C/75% RH and at 6 months for 40 °C/75% RH; applicant claims this increase was not "observed to directly correlate with any change in...dissolution"; no testing of final tablet (b) (4) proposed for specification • Tablet hardness is controlle (b) (4)

Craig
Bertha

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OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 209203	**Submission Type: 505(b)(2)**	**Established/Proper Name: allopurinol/lesinurad**
Applicant: Ardea Biosciences, Inc.	**Letter Date: 20-OCT-2016**	**Dosage Form: tablet**
Chemical Type: 5	**Stamp Date: 20-OCT-2016**	**Strengths: 300/200 and 200/200 mg allopurinol/lesinurad/tablet**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?	X		See biopharmaceutics-related comments below above risk assessment table

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☐	☒	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☐	☒	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	
10.	Locally acting drug[1]	☐	☒	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	
18.	Combination Product _____	☐	☒	

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B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
19.	Other_____	☐	☒	

Regulatory Considerations					
20.	USAN Names Assigned		☒	☐	
21.	End of Phase II/Pre-NDA Agreements		☒	☐	Biopharmaceutics team indicated that the proposed dissolution method appeared "reasonable" at EoP2 meeting
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☐	Unknown
24.	Comparability Protocol(s)[2]		☐	☒	
25.	Other_____		☐	☒	
Quality Considerations					
26.	Drug Substance Overage		☐	☒	
27.	Design Space	Formulation	☐	☒	
28.		Process	☐	☒	
29.		Analytical Methods	☐	☒	
30.		Other	☐	☒	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☐	N/A
33.	Alternative Microbiological Test Methods		☐	☐	Microbiology (or process) team will address this
34.	Process Analytical Technology[1]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☒	☐	
36.		Excipients	☐	☒	
37.		Microbial	☐	☐	Microbiology (or process) team will address this
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☒	☐	Lactose manufactured from bovine milk
40.	Novel Excipients		☐	☒	
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☒	
43.	Genotoxic Impurities or Structural Alerts (lesinurad)		☒	☐	(b) (4) of lesinurad); Of the extensive list of compounds screened related to lesinurad, compound (b) (4) is an observed drug substance impurity that contains and (b) (4), which is a structural alert for mutagenicity. In section on impurities (S.3), the applicant indicates that compound (b) (4) had "sufficient data to demonstrate lack of mutagenicity." There are other compounds in the exhaustive list that also include commonly recognized structural alerts as well (e.g., (b) (4) plus those that scored

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				lower than 5 in the genotox screens.
44.	Continuous Manufacturing	☐	☒	
45.	Other unique manufacturing process[1]	☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	☒	☐	GastroPlus (absorption model) was used to support the dissolution and allopurinol particle size acceptance criteria
47.	New delivery system or dosage form[1]	☐	☒	
48.	Novel BE study designs	☐	☐	For clinical pharmacology to address
49.	New product design[1]	☐	☒	
50.	Other_____	☐	☒	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	Expected (aquatic) Introduction Concentration less than 1 ppb for both APIs
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols	☒	☐	☐	
	FACILITY INFORMATION				
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA)	☐	☒	☐	Eight (8) sites are listed on 356h (three drug product manufacturing sites, four lesinurad related sites, and one allopurinol related site); the 356h fails to include the associated DMF number for [redacted] (b) (4))

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C. FILING CONSIDERATIONS					
	❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)				
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
	DRUG SUBSTANCE INFORMATION				
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☐	☒	☐	(b) (4) do not have a US Agents listed in their LoAs
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials	☒	☐	☐	Most information for the APIs is either provided by reference to the applicant's approved NDA 207988 (lesinurad) or to DMF (b) (4) (allopurinol)

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C. FILING CONSIDERATIONS					
	❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for	☒	☐	☐	There are some references made to the approved NDA 207988 for information (e.g., reference standards for lesinurad and related compounds); whether or not the stability data establishes the drug product stability through the proposed dating period will need to be determined by the drug product reviewer

C. FILING CONSIDERATIONS					
	product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				
	BIOPHARMACEUTICS				
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☐	Not Applicable. In accordance with the MOU between ONDP and OCP as of July 1, 2015, *in vivo* BA/BE studies will be reviewed by OCP. Two *in vivo* bioavailability / bioequivalence (BA/BE) studies (RDEA594-501; and ALLO-101) are performed to assess the relative BA of fixed dose combination (FDC) and single agent drug products and to evaluate the impact of dissolution on the *in vivo* PK and relative BA of allopurinol and oxypurinol respectively. These studies will be reviewed by the OCP
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☐	☐	☐	Yes The current submission is a 505(b)(2) application relying on the FDA's previous findings of safety and effectiveness for Zurampic® (Lesinuard tablets) and Zyloprim® (Allopurinol tablets). A BA/BE study (RDEA594-501) is performed comparing the two co-administered single agents(Alluprinol and Lesinurad) to FDC tablets (both strengths) to support the bridge. The developmental formulations are bridged by the proposed dissolution method. A change to non-functional film coating of the formulation studied in *in vivo* BA/BE study is made [(b) (4)] [(b) (4)] based coating (pivotal BE batch) to [(b) (4)] based coating (to-be-marketed product)]. This change is bridged by comparative dissolution by the proposed method as suggested in Type C meeting during IND (IND #119031; Meeting minutes dated January 19, 2016).
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☐	☐	No Both proposed FDC strengths (200mg/200mg and 200mg/300mg strength) are studied in *in vivo* BE study.

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FILING REVIEW

C. FILING CONSIDERATIONS					
					(b) (4) [redacted] (b) (4) [redacted] Further, the PBPK model is used to propose lesinurad and allopurinol particle size as well as dissolution specification which will be reviewed. However, the information provided to support biopharmaceutics portion of the application is not complete. Therefore, additional information necessary for biopharmaceutics review will be requested either via communication on filing determination (due Dec 19, 2016) or before 74 day letter is due or via 74 day letter (Jan 2, 2017). The Application is fileable from biopharmaceutics perspective (with IR). The biopharmaceutics information requests available in the document titled "**74 Day Letter Comments NDA 209203**" at the Sharepoint. These IR comments are also available at the end of this document.
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☐	Not Applicable (NA). The proposed product is an immediate release tablet.
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☐	Not Applicable (NA). The proposed product is an immediate release tablet.
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	☐	No
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☒	☐	☐	Executed batch records are translated (Swedish to English)

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FILING REVIEW

C. FILING CONSIDERATIONS					
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	☐	☐	☒	
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples	☐	☐	☒	

Biopharmaceutics Information Requests

We are in the process of reviewing your NDA and have identified the lack of some relevant information. In order to continue reviewing your submission, provide the following information/data.

1. *It is noted that mean % dissolved data along with observed ranges obtained with the proposed QC dissolution method are submitted for the to-be-marketed batches of both fixed dose combination (FDC) strengths [200mg/200mg - Lot # AAAE, AAAF, AAAG, PAAB;*

200mg/300mg – Lot # SAAF, SAAH, SAAG, RAAB; 0000(1), 3.2.P.5.4, Batch Analyses]; however, this is incomplete. Submit complete QC dissolution data (individual, mean, SD, %RSD, profiles) generated on these batches.

2. *Include the dissolution medium sampling volume and filter type that will be employed for filtration in the analytical procedure for dissolution (3.2.P.5.2). It is noted that dissolution method development report includes filter compatibility study in Appendix H (Method validation summary); however, details about drug filter compatibility study is not included in the validation report of the current submission [0000(1), 3.2.P.5.3]. Include the above information and provide updated report on "Validation of Analytical Procedure for Dissolution".*

3. *Provide details on the change made in process parameters for manufacturing* (b) (4) *batch used to demonstrate discriminating ability of the proposed QC dissolution method.*

4. *Provide dissolution similarity (e.g., f2 values) for all batches (comparing test and reference) used in the dissolution method discriminating ability study [0000(1), 3.2.P.2., Dissolution Method (AR-594-FDCA-004-1.0)].*

5. *Several hyperlinks in the dissolution method development report [0000(1), 3.2.P.2., AR-594-FDCA-004-1.0] do not work (e.g., references 11.9 to 11.13). Provide an updated dissolution method development report with active hyperlinks.*

6. (b) (4)

(b) (4)

7. *It is acknowledged that in silico PBPK datasets for the single agent Lesinurad drug product are submitted; however, the same is not submitted for the FDC drug product. In order to evaluate your modeling approach for particle size distribution and dissolution specifications, provide complete in silico PBPK datasets of the FDC product used for model development, optimization, validation, and application (e.g., Gastroplus compatible files including but not limited to *.mdb, *.cat, *.dsd, *.opd, *.spd, *.stc files). Include detailed model descriptions and raw data used for in silico modeling (model development, optimization, validation, and application) including but not limited to physicochemical parameters, in vitro dissolution profiles, in vivo plasma drug concentration time profiles, and virtual BE trials. Submit this information in module 5.3.1.3. As experienced with NDA 207988, if there is validation error on placing *.mdb files under 5.3.1.3, consider placing these files in module 1 (e.g., module 1.11). It is noted that *.mdb Gastroplus file is not submitted for cross referenced NDA 207988 (Lesinurad IR tablets). Submit this file under module suggested above. Also, submit datasets used for BE analysis performed in Phoenix WinNonlin.*

8. *It is stated in the PBPK report for the FDC product [0000(1), 5.3.1.3., SR16-019] that virtual dissolution profile used in virtual trial simulation to justify the proposed dissolution specification was generated by adjusting the identified sensitive time scale parameter A of the Weibull release profile. Provide the entire virtual % dissolved-time data in tabular format used in the simulation.*

9. *Elaborate on the use of plasma drug concentration time profile and pharmacokinetic data only from three subjects (subject 9002, 9003, and 9016; 0000(1), 5.3.1.3., SR16-019) for parameter sensitivity analysis (PSA) and simulation for justification on both the proposed particle size distribution and dissolution specifications. It is stated in the PBPK report for the FDC product about high variability of stomach emptying and the clearance and varying systemic clearance in these subjects and Table 29 and Table 30 are referenced. However, this is not evident from Table 29 and Table 30 [e.g., Clearnace (CL) column of Table 29 and Table 30]. Explain clearly the rationale on the use of PK data from three subjects versus all subjects from study 501 (Pivotal BE study) for parameter sensitivity analysis and simulation.*

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FILING REVIEW Attachment 1 – Risk Assessment

DP attribute/ CQA	Factors that can impact the CQA	O[1]	S[1, 2]	D[1]	FMECA RPN #	Comment & considerations
Appearance	• Quality of the formulation input materials • (b) (4) variability • (b) (4) process parameter variability • Tablet coating process parameter variability • Acceptance criteria for coating materials	2	1	2	4	• (b) (4)
Identification	• incorrect drugs formulated • no drug formulated	1	3	1	3	• Probability of occurrence should be low and detectability high if applicant adheres to GMPs: specification for drug substances include specific (FTIR) identification testing, consistent with Q6A • Severity of failure would depend on situation (incorrect or no drug present)[2] • Final drug product specifications include two non-specific orthogonal tests for the drug identity confirmation (consistent with Q6A)
Assay, degradation products	• input purity of APIs • input purity of excipients • incorrect amounts of APIs formulated • impurity formation due to interaction of drugs with (b) (4)	3	3	2	18	• Total impurities allowed in input APIs limited by respective specifications • Inorganic impurities and residual solvents also tested for input APIs with acceptance criteria proposed • Note heavy metal testing of lesinurad API has been removed during development with justification to be considered; applicant claims no (b) (4) used in allopurinol synthesis and provide test data to justify absence of routine testing • Excipients are of compendial quality, i.e., suitable for solid oral

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[2] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

	• degradation of drug substances due to [redacted] (protection from environment) • presence of [redacted] • CU problems (*vide infra*)					• dosage forms ([redacted] film coating prepared from compendial ingredients as well) • GMP adherence should prevent incorrect amounts of APIs formulated • Applicant has addressed API/excipient compatibility in P.2.1.2 (can also be gauged indirectly based on stability data provided in P.8) • Lesinurad [redacted] of lesinurad leads to [redacted] but subjecting drug substance to 70°C/75%RH for 1 month only leads to < [redacted]% of this [redacted]; allopurinol related compounds [redacted] and [redacted] (USP) are degradants with limits of NMT [redacted]% w/w each in the drug product specifications • [redacted]
Physical stability (solid state of APIs, dosage form)	• polymorphic or pseudo-polymorphic [redacted] conversion of drug substance	3	3	5	45	• Lesinurad is said to exist in two crystalline Forms 1 and 2 and [redacted] Form 2 is said to be the most [redacted]; Applicant claims to have performed "extensive crystal form screening" and mention only some irrelevant [redacted]; allopurinol is said to have "one known crystal form" but no references are provided in support of this statement and it is not clear that the FTIR identification test would be specific for the crystalline form • Note, FTIR (used for ID of drug substances) can distinguish the [redacted] (see S.1.3.5) of lesinurad • Applicant has not identified a [redacted]
Uniformity of dosage units	• lack of [redacted]	3	3	3	27	• [redacted] • Content uniformity is tested as part of drug product specification as per USP <905>

Microbial limits	• microbial load of input materials for formulation • microbial contamination during processing (b) (4) • microbial growth during shelf life	1	3	5	15	• Applicant proposes to test one batch of drug product annually for microbial limits (periodic quality indicator test or PQIT) • Applicant claims (b) (4) of drug substances and the dosage form render these as non-viable for microbial growth (data provided for drug product in P.5.6.7 as per Q6A) • The applicant indicates that historical data show the drug product complies with the microbial limits testing requirements of the USP
Drug Release or Dissolution	• polymorph conversion of APIs • changes in input excipients • API particle size change • (b) size • (b) (4) • tablet hardness	3	3	3	27	• Polymorph conversion is unlikely considering that the most (b) (4) of lesinurad is being formulated; allopurinol is said to only have a single crystalline form • Excipients are of compendial grade and in common use for solid oral dosage forms • API particle size acceptance criteria examined relative to a parameter sensitivity analyses for dissolution (see P.2.7.1.3.5.1) • Applicant notes that (b) (4) particle size does impact dissolution (see report AR-594-FDCA-004-1.0, p. 41); see minor impact of (b) (4) on dissolution in fig. 21 of P.2, Manufacturing Process Development • An increase (b) (4) was observed at 12 months for 25 °C/60% RH and 30 °C/75% RH and at 6 months for 40 °C/75% RH; applicant claims this increase was not "observed to directly correlate with any change in...dissolution"; no testing of final tablet (b) (4) proposed for specification • Tablet hardness is controlled (b) (4)

Craig Bertha

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Poonam Delvadia

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Office of Pharmaceutical Quality

NDA Reviewer Assignment Information

NDA # **209203**	Established/Proper Name: **allopurinol/lesinurad**
Dosage Form: tablets	Strengths: 200 mg lesinurad combined in fixed dose combinations with 200 mg or 300 mg of allopurinol/tablet
Applicant: Ardea Biosciences, Inc.	Lead Branch: Branch IV of DNDPII
BCS Class: Lesinurad class II/allopurinol class IV	Approximate Goal Date for Primary Review: 20-JUN-2017 (assuming standard review)
Submission Type: 505(b)(2)	Goal Date for Action: 20-OCT-2017
Chemical Type: 5	Cross Referenced Applications: IND 102128; IND 119031; NDA 207988; DMFs (b) (4)

A. PRODUCT/ PROCESS DESCRIPTION (Critical Information for Making Assignments)
The combination drug product is for treatment of hyperuricemia in gout patients. The allopurinol API is supported by DMF (b) (4) from a supplier that is also used for an approved allopurinol ANDA. Note the applicant's use of PK modeling to support the allopurinol particle size. The lesinurad API is the same as for Ardea's approved NDA 207988. The strength combinations of film-coated IR tablets are made with typical compendial-grade excipients in a (b) (4)

Office of Pharmaceutical Quality

NDA Reviewer Assignment Information

B. APPLICATION ELEMENTS				
	Initial Assessment	**Yes**	**No**	**Comments**
1.	Accelerated Review expected? (Priority or Breakthrough)		X	
2.	Narrow Therapeutic Index Drug		X	
3.	PET Drug, Drug Device Combination, Liposome product, Biosimiliar product, Novel Dosage Form, Emerging Technology		X	
4.	Specialty Population (i.e., young children and/or elderly)		X	
5.	Sterile Drug Product (Aseptic, Terminal, Parametric Release)		X	
6.	Use of Models for Release (IVIVC, dissolution models for real time release)	X		GastroPlus (absorption model) was used to support the dissolution and allopurinol particle size acceptance criteria
7.	DMF(s) referenced for drug substance?	X		DMF (b) (4) supports allopurinol
	Never reviewed			
	Previously reviewed - acceptable			
	Previously reviewed – new amendments	X		

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B. APPLICATION ELEMENTS				
	Initial Assessment	**Yes**	**No**	**Comments**
8.	Complex API (Polymeric molecules, Heterogeneous mixtures, Botanical, Antibody-Drug-Conjugate)		X	
9.	Real Time Release Testing, Continuous Manufacturing, PAT		X	
10.	EA Team: • NMEs • API with estrogenic, androgenic, or thyroid activity • API derived from plants or animals • Environmental Assessments		X	Applicant claims categorical exclusion under 21 CFR 25.31(b).

Summarized by *[Electronic Signatures]*

Signature and Date
Title: CMC Lead (DPARP) Print Name: Craig M. Bertha Signature and Date: Craig M. Bertha -S Digitally signed by Craig M. Bertha -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300103470, cn=Craig M. Bertha -S Date: 2016.10.26 06:33:35 -04'00'

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1 Approvals *[Electronic Signatures]*

Content Reviewers	J. Rondon, L. (OPRO/OE); D. Henry (OPRO/OE);); S. Miller (OPQ/ONDP); O. Stephens (OPQ/ONDP); IQA Steering Committee
Final Approval Signatures and Date	
Division Director, OPRO/OE & LPD, or Designee Title: Branch Chief, OPRO Organizational Excellence (Acting) Print Name: Jorge Rondon Signature and Date: Signature on file	
Authors Title: CMC-Lead/QAL, Branch III, DNDP-I, ONDP Print Name: Stephen Miller Signature and Date: Signature on file Title: Acting Branch Chief, OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII Print Name: Olen Stephens Signature and Date: Signature on file	

2 Document History

Version	**Effective Date**	**Lead Author** *and Working Group*	**Approving Official**	**Summary of Changes**
01	11/11/2015		J. Rondon	Initial

Craig Bertha

Digitally signed by Craig Bertha
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