CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212194Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

Drug Substance Retest Period [redacted] months for the drug substance packaged in the proposed commercial package when stored at [redacted] °C may be granted.

Drug Product Expiration Dating Period: Proposed 36 months for the drug product packaged in the proposed commercial package when stored between 2 °C and 25 °C (36 °F to 77 °F): may be granted

NDA 212194

Review # 1

Drug Name/Dosage Form	**Givosiran/ injection**
Strength	**189 mg/mL**
Route of Administration	**Subcutaneous injection**
Rx/OTC Dispensed	**Rx**
Indication	**Treatment of adults [redacted] with acute hepatic porphyria (AHP)**
Applicant	**Alnylam Pharmaceuticals Inc.**
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0002 (2)	*January 22, 2019*	*All CMC*
0003 (3)	*February 06, 2019*	*IR response Drug Product*
0005 (5)	*March 29, 2019*	*IR Response Facilities*
0009 (9)	*June 04, 2019*	*Labeling, Final Sections of the NDA*
0010 (10)	*June 12, 2019*	*IR Response Process, Microbiology*
0015 (15)	*August 27, 2019*	*IR Response Microbiology*
0019 (19)	*September 26, 2019*	*IR Response Microbiology*
0021 (21)	*October 08, 2019*	*IR Response Microbiology*
0022 (22)	*October 10, 2019*	*Labeling*
0023 (23)	*October 16, 2019*	*Labels*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Rohit Tiwari	Suong T. Tran
Drug Product	Rajiv Agarwal	Sherita McLamore

Process and Facility	Sridhar Thumma	David Anderson
Microbiology	Renee Marcsisin-Rogers	Elizabeth Bearr
Biopharmaceutics		Banu Zolnik
Regulatory Business Process Manager	Rabiya Haider	
Application Technical Lead	Anamitro Banerjee	
ORA Lead	NA	
Environmental	NA	

RELATED/SUPPORTING DOCUMENTS

DMFs:

DMF #	Type	Holder	Item Referenced	Status	Comments
(b) (4)	Type V		(b) (4)	Acceptable	
	Type III			Acceptable	Associated with DMF (b) (4). LOA is provided in DMF (b) (4). NDA 212194 does not have a LOA to DMF (b) (4).
	Type III			Acceptable The stopper meets the (b) (4) requirements in monograph 3.2.9 of the Ph. Eur. and JP 7.03, with the physicochemical tests as described in USP <381>	Reviewed by micro.
	Type III			Acceptable	
	Type III			Acceptable The vials meet the requirements of United States Pharmacopoeia (USP) <660>	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

IND	126094	Givosiran

CONSULTS

None

*See Microbiology review "**N212194MR01.docx**" dated 10/09/2019, and Process and Facility review "**N212194 Manufacturing R01.3 AQ.docx**" dated 09/12/2019 in Panorama for detailed evaluation of these sections.*

EXECUTIVE SUMMARY

The proposed drug product is supplied as a sterile, preservative-free solution containing 189 mg/mL givosiran in a single-dose, 2 mL Type 1 glass vial with a TEFLON®-coated stopper and a flip-off aluminum seal. The givosiran injection is available in cartons containing one single-dose vial each. Water for injection is the only excipient used in the manufacture of GIVLAARI.

Givosiran drug substance is a synthetic chemically modified small interfering ribonucleic acid (siRNA) that specifically targets 5'-aminolevulinate synthase 1 (ALAS1) messenger RNA (mRNA) via RNA interference mechanism. The sense and antisense strands of givosiran contain 21 and 23 nucleotides respectively. The 3'-end of the sense strand is covalently linked to the triantennary N-acetyl galactosamine (GalNAc) moiety (L96) through a phosphodiester linkage to enable delivery of the siRNA to hepatocytes. The drug substance is a white to pale yellow powder and manufactured by (b) (4) The applicant provided a detailed description of manufacturing process, in-process controls, and adequately characterized the drug substance and its related impurities. The manufacturing process (b) (4). The impurities in the givosiran specification are (b) (4). The applicant developed in-process acceptance criteria for (b) (4) the manufacture of givosiran drug substance. The drug substance specification includes (b) (4) The analytical methods and their acceptance criteria are risk-based including the criteria for impurities. The impurities limits are qualified in nonclinical studies and are acceptable. The batch analyses data for the PPQ batches meet the givosiran specification. The key analytical methods that test for purity, impurity, assay, and (b) (4) content are adequately described and validated, and are stability-indicating. The drug substance is packaged in (b) (4). The applicant provided up to (b) (4) months stability data at the proposed storage conditions. The proposed retest date of (b) (4) months when stored at (b) (4) °C is acceptable.

The drug product is composed of the drug substance dissolved in Water for Injection. No other excipients are used. (b) (4) The drug product is manufactured

by [redacted] The drug substance is [redacted]. The risk of the drug substance to [redacted] was mitigated by [redacted] controls mentioned in MBR. A batch size range of [redacted] L ([redacted] units) was proposed for commercial manufacturing based on the PPQ batches. No scale up is proposed.

The proposed drug product specifications include appearance, identity (using HPLC for both the duplex and the single strands), purity, assay, pH, osmolality, particulate matter, bacterial endotoxins, sterility, and volume in container. The associated analytical methods are appropriately described, and methods validated. The applicant provided risk assessment to justify omission of elemental impurities testing consistent with ICH Q3D. Batch data provided by the applicant shows no OOS data. The drug product is packaged as single dose configuration in 2 mL [redacted] clear glass vial closed with grey 13 mm TEFLON®-coated stopper and a flip-off aluminum seal and stored under refrigerated conditions.

The applicant provided up to 36 months stability data at the proposed storage conditions and appropriate stress data as per ICH guidelines. The proposed expiration dating period of 36 months when stored under refrigerated conditions/room temperature may be granted. The applicant provided appropriate post-approval stability protocol and commitment. The applicant would have, post-approval, up to 72 months at both conditions on 6 batches. Once approved, the yearly lots will be stored at room temperature. Given the stability characteristics at both storage temperatures the data supports the wider temperature range of 2 °C to 25 °C (36 °F to 77 °F).

All the facilities to be used for drug substance and drug product manufacturing, packaging, labeling and testing (release and stability) were evaluated and were found to have acceptable compliance history and experience in the proposed responsibilities. No major manufacturing process concerns that necessitates a PAI recommendation by OPF beyond the risks typically associated with this dosage form were identified. No PAI was recommended for these facilities. However, pre-approval inspections were performed for DP (Ajinomoto Althea, Inc.) and DS ([redacted]) manufacturing facilities by ORA based on their plans to inspect these facilities for surveillance. The PAIs resulted in minor FDA 483 observations pertaining to laboratory/manufacturing investigations which did not impact the manufacturing and testing capabilities of these facilities for NDA 212194. Based on PAIs, these facilities were deemed approvable.

Evaluation of the Quality Information

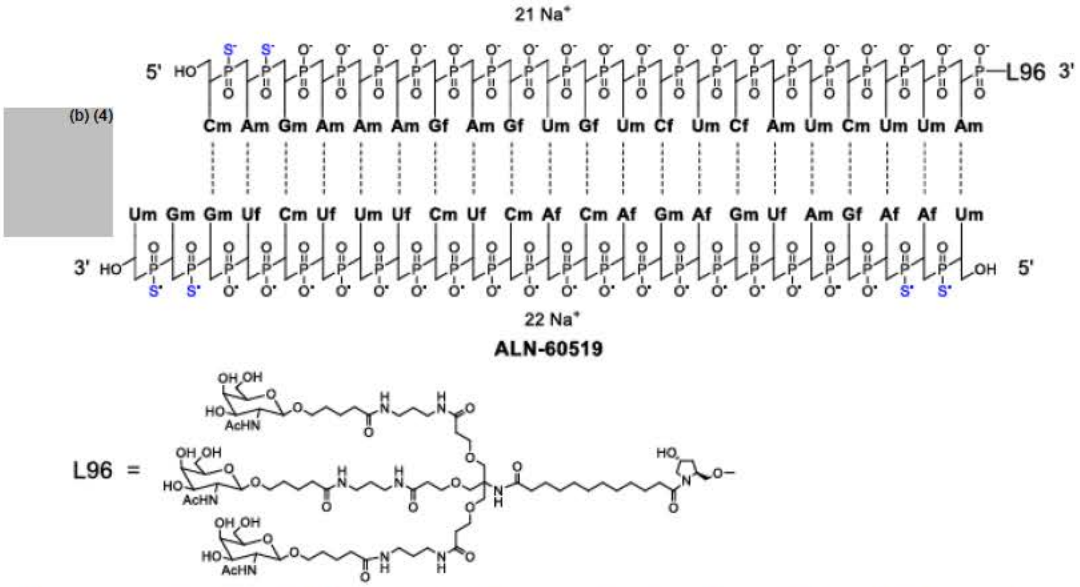
The proposed product was granted Orphan drug (August 29, 2016) Breakthrough Therapy (May 23, 2017) designations for the treatment of AHP; and granted Fast-track with rolling submission on August 08, 2018. The applicant requested priority review for this NDA.

Environment Assessment: *The applicant has submitted a claim for categorical exclusion, including a statement of no extraordinary circumstances. The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is acceptable. (conveyed by Dr. Raanan Bloom to the review team)*

Biowaiver Request: Not requested. As there were no changes to the drug product used in the Phase 3 clinical studies through the proposed commercial product, a bridging was not necessary, and the applicant did not conduct a clinical BA/BE study. Dr. Banu Zolnic indicated that a Biopharmaceutics reviewer is not needed for this NDA.

DRUG SUBSTANCE

The givosiran drug substance is a chemically synthesized double stranded oligonucleotide with a combination of 2'-F and 2'O-methyl nucleotides. It is a small interfering RNA (siRNA) formed (b) (4) of sense (21 nucleotides) and antisense (23 nucleotides) strands and targets aminolevulinic acid synthetase 1 (ALAS1). Givosiran is a hygroscopic, white to pale yellow powder and is freely soluble in water (357 mg/mL).



Abbreviations: Af = adenine 2'-F ribonucleoside; Cf = cytosine 2'-F ribonucleoside; Uf = uracil 2'-F ribonucleoside; Am = adenine 2'-OMe ribonucleoside; Cm = Cytosine 2'-OMe ribonucleoside; Gf=guanine 2'F ribonucleoside; Gm = guanine 2'-OMe ribonucleoside; Um = uracil 2'-OMe ribonucleoside; L96 = triantennary GalNAc (*N*-acetylgalactosamine)

USAN Name: **Givosiran**

	Drug Substance	(b) (4)
Molecular formula of the free acid	$C_{524}H_{694}F_{16}N_{173}O_{316}P_{43}S_6$	
Molecular formula of the sodium salt	$C_{524}H_{651}F_{16}N_{173}Na_{43}O_{316}P_{43}S_6$	
Molecular weight of the free acid	16,300.34 Da	
Molecular weight of the sodium salt	17,245.56 Da	

Drug Substance Manufacturing Process: (b) (4)

(b) (4)

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

(b) (4)

The applicant provided standard stability commitment.

The applicant is proposing a retest period of (b) (4) months for the drug substance packaged in the proposed commercial package when stored at (b) (4) °C± 5°C. This is acceptable.

DRUG PRODUCT

Givosiran drug product (DP) is a sterile solution, containing 189 mg/mL givosiran (equivalent to 200 mg/mL givosiran sodium), a double-stranded small interfering ribonucleic acid (siRNA), formulated in water for injection (WFI).

Givosiran DP is a sterile, preservative-free, colorless to yellow solution for subcutaneous injection. It is supplied as a 1-mL solution in a 2-mL Type I glass vial with a teflon-coated (b) (4) stopper and an aluminum flip-off cap. Givosiran DP is for single use.

Drug Product Composition: Composition of the proposed givosiran drug product is provided in the Table P.1 below. All the ingredient except for the drug substance are compendial. (b) (4) The WFI was used (b) (4) .

Table P.1: Composition of the Givosiran Drug Product

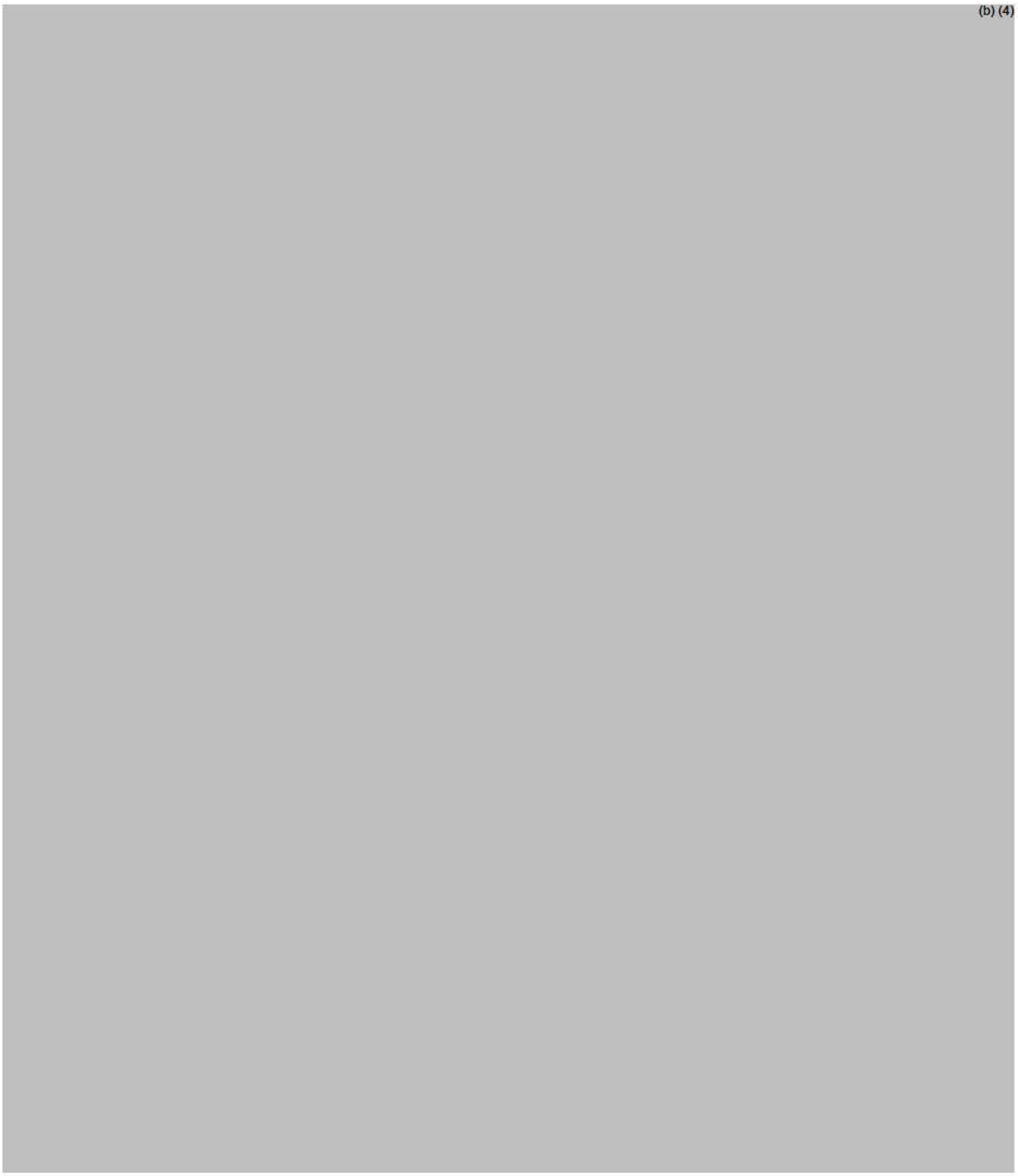
Component	Concentration (mg/mL)	Content per vial	Batch Formula	Function	Quality Standards
Givosiran sodium	189 (equiv. to 200 givosiran Na salt)	189 (equiv. to 200 givosiran Na salt)	(b) (4)	Active ingredient	Manufacturer's Specifications
Water for injection, sterile	(b) (4)			(b) (4)	Ph. Eur., USP/NF, JP

Drug Product Manufacturing Process: (b) (4)

(b) (4)

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

(b) (4)



Drug Product Container Closure System:

The givosiran drug product is packaged in a single use, 2 mL (b) (4) clear glass vial (Type 1 glass conforms to USP <660>). The vial closure is a gray 13 mm Teflon coated (b) (4) stopper, which meets physicochemical tests as described in the USP <381>. The overseals for the stoppers are 13 mm tamper evident flip off matte caps. The applicant provided LOA for the DMFs for these components.

The applicant also provided extractables and leachables analysis (volatile sulfides, residue on evaporation, and extractable zinc, extractable heavy metals, reducing substances, ammonia etc. and all test results were within the specified limits (refer to the DMF (b) (4)).

In addition, USP <87> in-vitro biological reactivity test is conducted on the stopper extract and extract pass the test.

It can be concluded that the physical and chemical properties of the Type I, 2-mL clear glass vial and the Teflon® (b) (4) elastomer stopper are suitable for use with Givosiran DP.

Stability Study on Drug Product:

Thermal Stress (60 °C for 14 days, samples collected day 1, 3, 7, 10 and 14): Appears to be stable with minor decrease in purity (total degradation trends from (b) (4)% to (b) (4)% over 14 days by denaturing AX-HPLC, no other trends).

Oxidative Stress (3% H_2O_2 for 24 h): (b) (4)% decrease in purity by denaturing AX-HPLC with corresponding increase in impurities RRT = (b) (4) and RRT> (b) (4).

Photostability: per ICH Q1B (1.2 million lux hours, 200 Watts/m^2 UV): Appears to be stable with minor decrease in purity. As a conservative approach, the applicant is recommending storage in original packaging until ready for use.

Thermal Cycling Stress Study/Freeze-Thaw Testing (4 cycles of -20 °C for 3 days, then 3 day 40°C/75%RH – 12 days cumulative at each condition): No effect observed.

Stability data for registration batches is summarized below:

Note: The stability program includes givosiran DP stored in the inverted orientation; due to maximal contact of the aqueous givosiran DP with the elastomer stopper, this orientation is considered worst-case.

The following is the summary of stability evaluation:

Long Term Storage Conditions/Refrigerated Conditions (2 °C – 8 °C/ambient RH): 36 months data for 1 batch and 18 months data for 2 stability batches. Also provided 3 months data for 3 PPQ batches. Minor changes in purity and degradation by both denaturing HPLC methods. No OOS result.

Long Term Storage Conditions (25 °C/60% RH): 36 months data for 1 batch and 18 months data for 2 stability batches. Also provided 3 months data for 3 PPQ batches. Minor changes in purity and degradation by both denaturing HPLC methods. No OOS result.

Accelerated Storage Conditions (40 °C/75% RH): 6 months data for 3 stability batches and 3 months for the 3 PPQ batches. Minor changes in purity and degradation by both denaturing HPLC methods. No OOS result. No OOS results.

The applicant provided stability data for both refrigerated (2 ºC -8 ºC) and 25 ºC/60%RH. The applicant indicated that since the room temperature is considered a worst case scenario, the post approval protocol will include stability studies for future lots at room temperature. The applicant will continue the current study for 72 months. standard stability commitment. The protocol is shown below (Table P.8).

Table P.8: Testing Plan for Stability Commitment Program

Attribute	Method[a]	Acceptance Criterion	Storage time (months)[b]										
			0	3	6	9	12	18	24	36	48	60	72
Appearance	Visual Inspection	Clear, colorless to yellow solution essentially free of particulates	S	S	S	S	S	S	S	S	S	S	S
Purity, non-denaturing													
Duplex	IPRP HPLC UV (non-denaturing)	NLT (b) (4) area%	S	S	S	S	S	S	S	S	S	S	S
Total impurities		NMT area%	S	S	S	S	S	S	S	S	S	S	S
Purity, denaturing IPRP													
Total single strands		NLT (b) (4) area%	S	S	S	S	S	S	S	S	S	S	S
Total impurities		NMT area%	S	S	S	S	S	S	S	S	S	S	S
Specified impurities: sum of area% (X.X) for all other peaks ≥ (b) (4) area%	IPRP-HPLC UV (denaturing)												
(b) (4)		NMT (b) (4) area%	S	S	S	S	S	S	S	S	S	S	S
		NMT area%	S	S	S	S	S	S	S	S	S	S	S
		NMT (b) (4) area%	S	S	S	S	S	S	S	S	S	S	S
		NMT area%	S	S	S	S	S	S	S	S	S	S	S
Unspecified impurities		No peak outside of the specified ranges (b) (4) area%	S	S	S	S	S	S	S	S	S	S	S

Attribute	Method[a]	Acceptance Criterion	Storage time (months)[b]										
			0	3	6	9	12	18	24	36	48	60	72
Purity, denaturing AX													
Total single strands		NLT (b) (4) area%	S	S	S	S	S	S	S	S	S	S	S
Total impurities		NMT area%	S	S	S	S	S	S	S	S	S	S	S
Specified impurities: sum of area% (X.X) for all other peaks ≥ (b) (4) area%	AX-HPLC UV (denaturing)												
(b) (4)		NMT (b) (4) area%	S	S	S	S	S	S	S	S	S	S	S
		NMT area%	S	S	S	S	S	S	S	S	S	S	S
		NMT area%	S	S	S	S	S	S	S	S	S	S	S
		NMT area%	S	S	S	S	S	S	S	S	S	S	S
Unspecified impurities		No peak outside of the specified ranges (b) (4) area%	S	S	S	S	S	S	S	S	S	S	S
Assay	UV absorption	(b) (4) mg/mL (free acid form)	S	S	S	S	S	S	S	S	S	S	S
Osmolality	USP<785>, EP 2.2.35	(b) (4) mOsm/kg	S	S	S	S	S	S	S	S	S	S	S
pH	USP<791>, EP 2.2.3	(b) (4)	S	S	S	S	S	S	S	S	S	S	S
Particulate matter													
≥10 µm	USP <788>	NMT (b) (4) per container	S	NS	NS	NS	S	NS	S	S	S	S	S
≥25 µm		NMT (b) (4) per container	S	NS	NS	NS	S	NS	S	S	S	S	S
Bacterial endotoxins	USP <85>	NMT (b) (4) EU/mL	S	NS	NS	NS	S	NS	S	S	S	S	S
Sterility	USP <71>	No growth	S	NS	NS	NS	NS	NS	S	S	S	S	S
CCIT	Dye ingress	No evidence of dye ingress	NS	NS	NS	NS	S	NS	NS	NS	NS	NS	NS

[a] When harmonized compendial methods are used, they will be applicable to the ICH regions in accordance to ICH Q4B guideline

[b] depending on the results of ongoing supplementary studies performed at ICH Zone IVb conditions, future shelf life verification may be performed at the more extreme condition of 30°C±2°C/70%RH±5%RH

Abbreviations: as=antisense; AX=anion-exchange; FLP=full-length product; HPLC=high-performance liquid chromatography; NS=Not scheduled; NLT=not less than; NMT=not more than; Ph. Eur.=European Pharmacopeia; S=samples stored at 2°C-8°C (ICH refrigerated), and 25°C±2°C/60% RH±5%RH (ICH Zone II); ss=sense strand; USP=United States Pharmacopoeia; UV=ultraviolet

The applicant is proposing an expiration dating period of 36 months for the drug product packaged in the proposed commercial package when stored between 2 °C and 25 °C (36 °F to 77 °F).

(b) (4)

FACILITIES

Drug substance manufacturing, packaging and testing facilities are listed below:

Site/address	FEI	Responsibility	Recommendation
(b) (4)		Drug substance manufacturing and release testing	Acceptable based on pre-approval inspection.
		Drug substance bioburden testing	Acceptable based on profile.

Drug product manufacturing, packaging and testing facilities are listed below:

Site/address	FEI	Responsibility	Recommendation
Ajinomoto Althea, Inc., 11040 Roselle St. San Diego, CA 92121	3004575449	Drug product manufacture	Acceptable based on pre-approval inspection.
(b) (4)		Drug product release testing	Acceptable based on profile.
		Drug product secondary packaging and labeling	No Evaluation Necessary.

Refer to Process/facility integrated review (Facility Review) for detailed assessment of each facility and the basis for recommendation.

LABELING

The quality sections of the Prescribing Information, sections 2 DOSAGE AND ADMINISTRATION, 3 DOSAGE FORMS AND STRENGTH, 11 DESCRIPTION, and 16 HOW SUPPLIED/STORAGE AND HANDLING provided by the applicant appear appropriate. The applicant provided adequate manufacturer information. The final version of this document will be cleared by the clinical division following input from all the review divisions and interactions with the applicant.

The applicant provided carton and container label appropriate with the proposed dosage form. The labels indicate the proposed brand name (GIVLAARI), drug substance proprietary name, strength, dosage form, route of administration, salt equivalency statement, storage temperature range, (b) (4), NDC number, space for lot and expiry date, and manufacturer information.

The Prescribing Information and Carton and Container labels have been revised per Labeling Guidance January 2018 and they are adequate from a CMC standpoint.

(b) (4)

Final Risk Assessments

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H	(b) (4)	Acceptable	Controls are in place and continue stability monitoring post approval
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place and continue stability monitoring post approval
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	Controls are in place, continue stability monitoring post approval
Physical stability (solid state)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	Controls are in place, continue stability monitoring post approval
Uniformity of Dose (Fill volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		Acceptable	Controls are in place, continue stability monitoring post approval
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	Controls are in place, continue stability monitoring post approval
pH (High)	• Formulation • Container closure • Raw materials • Process parameters	L		Acceptable	Controls are in place, continue stability monitoring post approval

			(b) (4)		
	• Scale/equipment • Site				
pH (Low)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	Controls are in place, continue stability monitoring post approval
Particulate Matter	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	M		Acceptable	Controls are in place, continue stability monitoring post approval
Leachables extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	Change in container closure requires USP <87> testing.
Appearance (color/turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	Controls are in place, continue stability monitoring post approval

Recommendation Page

Drug Substance: Approval

Primary Reviewer: Rohit Tiwari Date: 08/06/2019
Secondary Reviewer: Suong T. Tran Date: 08/06/2019

Drug Product: Approval

Primary Reviewer: Rajiv Agarwal Date: 09/24/2019
Secondary Reviewer: Sherita McLamore Date: 10/09/2019

Process and Facility: Approval

Primary Reviewer: Sridhar Thumma Date: 09/16/2019
Secondary Reviewer: David Anderson Date: 09/16/2019

Microbiology: Approval

Primary Reviewer: Renee Marcsisin-Rogers Date: 10/15/2019
Secondary Reviewer: Elizabeth Bearr Date: 10/15/2019

Application Technical Lead: Approval

Anamitro Banerjee Date: 10/15/2019

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/

ANAMITRO BANERJEE
10/21/2019 02:26:05 PM

ROHIT V TIWARI
10/21/2019 04:38:33 PM

SUONG T TRAN
10/22/2019 09:27:31 AM

RAJIV AGARWAL
10/22/2019 09:28:48 AM

SHERITA D MCLAMORE
10/22/2019 10:49:27 AM

SRIDHAR N THUMMA
10/22/2019 11:24:00 AM

DAVID D ANDERSON
10/23/2019 10:41:19 AM

RENEE A MARCSISIN-ROGERS
10/24/2019 07:13:14 AM

ELIZABETH R BEARR
10/24/2019 09:42:03 AM