



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Review Memorandum

May 2, 2023

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Subject: STN 125775/0

Product Name AREXVY, a Respiratory Syncytial Virus Vaccine Recombinant, Adjuvanted (RSVPreF3 Older Adults [OA] vaccine)

Applicant GlaxoSmithKline Biologicals SA (GSK)

Proposed Indication For active immunization for prevention of RSV-associated lower respiratory tract disease (LRTD) in adults aged 60 years and older

Cross-reference(s) BB-IND 018540 AS01E Adjuvant System
DMF (b) (4) Gray stoppers
DMF (b) (4) MPL manufacturing facility
DMF (b) (4) QS-21 manufacturing facility

Review of the Chemistry, Manufacturing, and Control information relevant to AS01E adjuvant submitted in the Biologics License Application

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1.0 EXECUTIVE SUMMARY

1.1 RESPIRATORY SYNCYTIAL VIRUS VACCINE RECOMBINANT, ADJUVANTED

AREXVY is a Respiratory Syncytial Virus (RSV) sub-unit recombinant vaccine consisting of two components: the RSVPreF3 antigen and GSK's proprietary Adjuvant System, AS01E, also referred to as RSVPreF3 Older Adults (OA) vaccine. AREXVY is a preservative-free suspension for intramuscular injection.

The RSVPreF3 antigen is an engineered RSV F protein purified from CHO cells with (b) (4)

. The RSVPreF3 antigen is filled into single-use vials and lyophilized.

The vaccine is presented in two mono-dose vials: one vial containing the RSVPreF3 protein in a lyophilized form (120 µg/dose) and the second vial containing liquid AS01E Adjuvant System (AS01E Adjuvant, 0.5 mL/dose). The content of the AS01E vial is used to reconstitute the content of the RSVPreF3 vial prior to injection of AREXVY.

The 0.5 mL dose is administered intramuscularly with a needle and syringe. The proposed indication is for active immunization for the prevention of lower respiratory tract disease caused by respiratory syncytial virus A and B (RSV-A and RSV-B) subtypes in adults 60 years of age and older. The review of the manufacturing and associated activities for the RSVPreF3 antigen (Drug Substance) is provided by Dr. Judy Beeler.

AREXVY is expected to be the first RSV-A vaccine approved for use in the US and the second vaccine approved in the US that includes the AS01 Adjuvant System in its formulation. The first approved vaccine with AS01 Adjuvant system was SHINGRIX (2017, STN 125614).

This current review covers the AS01E adjuvant Drug Product.

1.2 AS01E ADJUVANT DRUG PRODUCT (DP)

1.2.1 GENERAL DESCRIPTION, COMPOSITION, AND MODE OF ACTION OF AS01E ADJUVANT

AS01E Adjuvant System contains immune enhancers MPL (3-O-desacyl-4'-monophosphoryl lipid A) and QS-21 (*Quillaja saponaria* Molina) combined with liposomes that are prepared using two lipids, DOPC (dioleoyl phosphatidylcholine) and cholesterol; the liposomes are suspended in a phosphate buffer. AS01E Adjuvant System is formulated containing 25 µg of each of the immune enhancers per 0.5 mL dose (Table 1). Information regarding MPL, QS-21, and DOPC excipients were submitted and approved

by FDA in the context of Zoster Vaccine Recombinant, Adjuvanted (Shingrix) registration file and, therefore, these excipients are not considered as novel.

The AS01E adjuvant is presented in a single dose 3 mL glass vial (Type (b) (4) closed with rubber stopper and aluminum cap.

AS01E components and AS01E composition

MPL is a detoxified endotoxin obtained from *Salmonella minnesota* (b) (4). (b) (4) doing business as GSK Vaccines (b) (4). MPL is produced by (b) (4). MPL is (b) (4).

QS-21 is a saponin purified from the bark of the South American tree *Quillaja saponaria* Molina. QS-21 powder is manufactured by (b) (4). QS-21 powder is a non-compendial excipient and is not described in pharmacopoeia. QS-21 powder is (b) (4).

DOPC is a semi-synthetic phospholipid. (b) (4). DOPC is manufactured by (b) (4). DOPC is (b) (4).

Cholesterol (semi-synthetic, (b) (4)).

Cholesterol is (b) (4).

Table 1 Composition of AS01E adjuvant

Ingredients	Quantity (per 0.5 ml dose) ¹	Function	Reference/Monograph Standard
3-O-desacyl-4'-monophosphoryl lipid A (MPL)	25 µg	(b) (4)	(4)
Purified Quillaja Saponin ² (QS-21)	25 µg		
Dioleoyl phosphatidylcholine (DOPC)	500 µg		
Cholesterol	125 µg		
Disodium phosphate anhydrous (Na ₂ HPO ₄)	150 µg		
Potassium dihydrogen phosphate (KH ₂ PO ₄)	(b) (4)		
Sodium chloride (NaCl)	(b) (4)		
Water for injection	(b) (4)		

(b) (4)

dose of 0.5 ml.

²Purified *Quillaja* Saponin is the full name for QS-21.

BIOLOGICAL ACTIVITY/MODE OF ACTION

AS01E induces a transient activation of the innate immune system by two immune enhancers MPL (Lipid A) (b) (4) and by QS-21 (b) (4)

It is believed that QS-21 (b) (4)

Nonclinical studies performed by the company indicated that both MPL and QS-21 are required to (b) (4)

IMPORTANT PHYSICOCHEMICAL AND BIOLOGICAL PROPERTIES OF AS01E ADJUVANT

(b) (4)

1.2.2 SUMMARY OF THE MANUFACTURE OF AS01E ADJUVANT AND AS01E FINAL CONTAINER SPECIFICATIONS

Manufacturers: Production, quality control, and stability testing of intermediates, (b) (4) and QS-21 (b) (4) are performed by GlaxoSmithKline Biologicals (GSK) at their (b) (4) facility (Belgium). Formulation and filling of AS01E, labeling, packaging, quality control and stability testing, and quality control testing of the final product are performed by GSK at (b) (4) facility and at the GSK's facility (b) (4). Labeling and packaging and quality control testing of the final product (post packaging identity test of the final product containing labelled and inspected vials of RSVPreF3 Lyo and AS01E) may be performed by (b) (4) GSK) at their facility in (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

All analytical procedures used for the BLA and for commercial supply of AS01E adjuvant Final Container (FC), and for quality control of (b) (4), have been adequately qualified. The summaries of the qualification results demonstrate specificity, precision, accuracy, robustness, and reproducibility for each evaluated analytical assay, indicating that they are suitable for the intended use.

AS01E Final Container Specifications

Table 2 AS01E Final Container release specifications

Tests	Specifications
Description	Opalescent, colorless to pale brownish liquid (b) (4)
(b) (4)	(b) (4)
Volume	(b) (4)
MPL content (b) (4)	(b) (4)
QS-21 content (b) (4)	(b) (4)
(b) (4)	(b) (4)
Cholesterol content (b) (4)	(b) (4)
DOPC content (b) (4)	(b) (4)

STN 125775 AREXVY
CMC: AS01E Adjuvant Drug Product
Marina Zaitseva

Tests	Specifications
(b) (4)	(b) (4)
Sterility test (b) (4)	Absence of growth
Sterility test (b) (4)	Absence of growth

(b) (4)

The first two steps are relatively straightforward. The third step is more complex because it requires the identification of the specific factors that contribute to the problem. This can be done through a variety of methods, including interviews, focus groups, and surveys. Once the factors have been identified, the next step is to develop a plan of action. This plan should outline the specific actions that will be taken to address the problem, as well as the resources that will be needed to implement the plan.

1. **Identify the subject and the main idea of the text.**
 2. **Summarize the text in your own words.**
 3. **Identify the author's purpose and tone.**
 4. **Identify the main supporting points and evidence.**
 5. **Identify the conclusion and any recommendations.**

(b) (4)

(b) (4)




1.2.4 CONCLUSION AND RECOMMENDATION

In summary, the CMC information, and the data relevant to the AS01E adjuvant manufacture presented in this BLA is complete and adequate to demonstrate that the AS01E adjuvant is manufactured under GMP by a validated process and the AS01E adjuvant meets accepted standards of purity and quality as required for an adjuvant or constituent material as per 21 CFR 610.15. The AS01E CMC information presented in the the BLA supports its use for the manufacture of RSVPreF3 Older Adults [OA] vaccine [AREXVY].


2.0 INFORMATION REQUESTS (IR) SUBMITTED TO GSK RELATED TO AS01E MANUFACTURING PROCESS, COMPANY'S UPDATE AND CONCLUSIONS

2.1 INFORMATION REQUESTS

1. In IR9 (February 2, 2023) Question 1, the firm was asked to provide the report on the toxicological assessment for the (b) (4)
- 

7 Pages have been determined to be not releasable: (b)(4)

(b) (4)



3.0 FULL REVIEW MEMO

This memo covers the following sections in 3.2.P Drug Product [AS01E Adjuvant system, injection, GSK biologics]:

- 3.2.P.1 Description and Composition of the Drug Product
- 3.2.P.2 Pharmaceutical Development
- 3.2.P.3 Manufacture
- 3.2.P.4 Control of Excipients
- 3.2.P.5 Control of Drug Product
- 3.2.P.6 Reference Standards or Materials
- 3.2.P.7 Container Closure System
- 3.2.P.8 Stability
- 3.2.R Regional Information (relevant to AS01E adjuvant)

4.2.1.1 Nonclinical studies: Primary pharmacodynamics
4 2 1 3 Nonclinical studies: Pharmacology
4.2.2.3 Nonclinical studies: Distribution

ABBREVIATIONS

(b) (4)

CPPs, Critical Process Parameters

CQAs, Critical Quality Attributes

DOPC (dioleoyl phosphatidylcholine)

(b) (4)

FC, Final Container

(b) (4)

GMP, Good Manufacturing Practices

(b) (4)

IPC, In-Process Parameters

(b) (4)

MPL (Monophosphoryl Lipid A)

NMT, No More Than

PDE, Permitted Daily Exposure

PETG, polyethylene terephthalate glycol containers

PPQ, Process performance Qualification

QD, quality decision tests

QS-21 (b) (4), QS-21 (b) (4)

TRA, Technical risk assessment

TTC, Threshold of Toxicological Concern

(b) (4)

3.1 DESCRIPTION AND COMPOSITION OF AS01E DP

DESCRIPTION, AS01E

The AS01E Adjuvant System is composed of two immune enhancers, QS-21 (a triterpene glycoside purified from the bark of the tree *Quillaja saponaria* Molina) and MPL (3-Odesacyl- 4'-monophosphoryl lipid A), using liposomes as a vehicle. The liposomes are composed of dioleoyl phosphatidylcholine (DOPC) and cholesterol in a phosphate buffered saline solution (Table 3). The pharmaceutical form of the AS01E Adjuvant System is an opalescent, colorless to pale brownish liquid suspension. The commercial presentation of AS01E is a mono-dose vial.

Table 3 Composition of AS01E adjuvant

Ingredients	Quantity (per 0.5 ml dose) ¹	Function	Reference/ Monograph Standard
3-O-desacyl-4'-monophosphoryl lipid A (MPL)	25 µg	(b) (4)	(4)
Purified Quillaja Saponin ² (QS-21)	25 µg		
Dioleoyl phosphatidylcholine (DOPC)	500 µg		
Cholesterol	125 µg		
Disodium phosphate anhydrous (Na ₂ HPO ₄)	150 µg		
Potassium dihydrogen phosphate (KH ₂ PO ₄)	(b) (4)		
Sodium chloride (NaCl)	(b) (4)		
Water for injection	(b) (4)		

(b) (4)

dose of 0.5 ml.

²Purified *Quillaja* Saponin is the full name for QS-21.

AS01E excipients

- MPL, 3-O-desacyl-4'-Monophosphoryl Lipid A (MLA), (b) (4) from the *Salmonella Minnesota* (b) (4). It is a detoxified endotoxin. MPL's function in the AS01 Adjuvant System is to enhance the immune response to the presented antigen(s).
- QS-21 is a saponin purified from the bark of the South American tree *Quillaja Saponaria* Molina. QS-21's function in the AS01 Adjuvant System is to enhance the immune response to the presented antigen(s).
- Dioleoyl phosphatidylcholine (DOPC) (1, 2-Dioleoyl-sn-glycero-3-phosphocholine) is a semi-synthetic phospholipid. (b) (4)
- Cholesterol is a semi-synthetic cholesterol (b) (4)
- Water for injection is the solvent in the AS01 Adjuvant System

- Na₂HPO₄, KH₂PO₄, NaCl are the buffering agents (b) (4)

The details of the manufacture of MPL, QS-21, and DOPC are not provided in the BLA. The manufacturing of QS-21 powder and of DOPC was described in detail in SHINGRIX BLA. The manufacture of MPL was described in detail in Cervarix™ (Human Papilloma virus vaccine) approved in the United States (STN 125259). The testing and control of MPL is described in (b) (4). Per agreement between CBER and GSK during pre-BLA CMC meeting (CRMTS# 14094 July 20, 2022), GSK submitted an example of Certificates of Analysis (COA) for the MPL lots used in the manufacture of AS01E adjuvant and specifications, analytical methods, and validation of analytical methods pertinent to CMC of QS-21 powder and DOPC including COAs for (b) (4) of QS-21 and DOPC.

UNII codes and substance names related to AS01E (Table 4) are being published on the Structural Product Labeling website at <https://www.fda.gov/industry/fda-resources-data-standards/structured-product-labeling-resources>

Table 4 AS01E components, abbreviations as appear in the BLA, and UNII codes

ADJUVANT SUSPENSION COMPONENT	ABBREVIATION/ FORMULA USED IN BLA	UNII
MONOPHOSPHORYL LIPID A (b) (4)	MPL	(b) (4)
QUILLAJA SAPONIN	QS-21	
1,2-DIOLEOYL-SN-GLYCERO-3-PHOSPHOCHOLINE	DOPC	
CHOLESTEROL	NA	
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS	Na ₂ HPO ₄	
MONOBASIC POTASSIUM PHOSPHATE	KH ₂ PO ₄	
SODIUM CHLORIDE	NaCl	
WATER	NA	

3.2 PHARMACEUTICAL DEVELOPMENT

3.2.1 FORMULATION DEVELOPMENT

(b) (4)

14 Pages have been determined to be not releasable: (b)(4)

3.2.P.3.4 Critical Process Parameters AS01 in the BLA and that are reviewed in section 2.3.4 Controls of the Critical Steps and Intermediates in this review memo.

Regarding sterility, bioburden, endotoxin, and (b) (4) testing of AS01E DP batches

- (b) (4) .
- Endotoxin test (b) (4) is performed on (b) (4) QC release test, (b) (4) as a QC monitoring test. (b) (4)
- The bioburden test is carried out as a QC monitoring test (b) (4) as a QC release test. (b) (4)
- The sterility test is performed (b) (4) as a QC release test.
- AS01E FC lots were tested for (b) (4) during product development and results met acceptance criteria. Based on the overall control strategy, a microbial and endotoxin risk assessment of the manufacturing process, the large amount of accumulated data, and to reduce animal testing, (b) (4) testing will not be performed on PPQ lots or on future commercial lots.

Reviewer assessment: The strategy for safety testing of AS01E batches based on sterility, bioburden, and endotoxin is acceptable. I agree that the data accumulated during process development, including results from (b) (4) AS01E lots that passed the pyrogenicity test in rabbits (see subsection Pyrogenicity in rabbits in Section 3.2.2 in this memo), show that the controls in place are sufficient to allow omitting the pyrogenicity testing of AS01E PPQ lots and future AS01E commercial lots.

3.2.3.7 CONTAINER CLOSURE SYSTEM FOR AS01E FC, (b) (4)

This section describes the following container closure system: 3 mL vials AS01, (b) (4) (all in Section 3.2.P.2.4 in the submission).

(b) (4)

10 Pages have been determined to be not releasable: (b)(4)

(b) (4)

3.3 MANUFACTURE, AS01E

3.3.1 MANUFACTURING AND TESTING FACILITIES

The CMC facilities used for the manufacture and testing of AS01E are shown in Table 10.

Table 10 Information on Facilities Involved in the Manufacture, Testing and Warehousing of Commercial AS01E Adjuvant Lots

Site Name/Site address	Specific Manufacturing Responsibilities or Type of Testing
GlaxoSmithKline SA (b) (4)	<ul style="list-style-type: none"> - Production of Intermediates¹ - Formulation and Filling of AS01E FC - Labelling, Packaging and Visual Inspection - Quality Control and Stability Testing of Intermediates¹ - Quality Control and Stability Testing of AS01E FC - Quality Control Testing of final product² - Warehouse operations
GlaxoSmithKline Vaccines (b) (4)	<ul style="list-style-type: none"> - Formulation and Filling of AS01E - Labelling, Packaging and Visual Inspection - Quality Control and Stability Testing of AS01E FC - Quality Control Testing of final product² - Warehouse operations
(b) (4)	<ul style="list-style-type: none"> - Labelling and Packaging - Quality Control Testing³ of final product² - Warehouse operations
(b) (4)	<ul style="list-style-type: none"> - Warehouse operations
(b) (4)	<ul style="list-style-type: none"> - Warehouse operations

Site Name/Site address	Specific Manufacturing Responsibilities or Type of Testing
(b) (4)	

1. (b) (4)
2. Final product: Combo box containing labelled and inspected vials of RSVPreF3 Lyo and AS01E
Quality Control testing of Packaged product limited to the post-packaging Identity test.
3. Quality Control testing at this site is limited to post packaging Identity test which confirms the
product contained in the vial matches the information on the label.

3.3.2 DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

3.4 CONTROL OF EXCIPIENTS

The following excipients used to manufacture AS01 are well-known and widely used: cholesterol, disodium phosphate anhydrous, potassium dihydrogen phosphate, sodium chloride and water for injection; therefore, they are not considered as novel.

Information regarding 3-O-desacyl-4'-monophosphoryl lipid A (MPL), purified *Quillaja* saponin (QS-21) and dioleoyl phosphatidylcholine (DOPC) were submitted and approved by FDA in the context of the SHINGRIX BLA. Therefore, they are not considered as novel.

Review of excipients is provided in two sections: (b) (4) excipients (MPL, cholesterol, disodium phosphate anhydrous, potassium dihydrogen phosphate, sodium chloride, and water for injection) and (b) (4) excipients (DOPC and QS-21).

3.4.1 (b) (4) EXCIPIENTS, MPL, CHOLESTROL, KH_2PO_4 , NaCl , Na_2HPO_4 , AND WFI

➤ MPL

3-O-Desacyl-4-monophosphoryl lipid A is produced by GSK and complies with the current edition of the (b) (4) which covers the justification of the specification. Batches will comply with the requirements of the relevant (b) (4) if tested using the (b) (4) methods of analysis.

The Certificate of Analysis for MPL (b) (4) is provided in Annex 1, all analytical attributes are within specification, the expiration date for this lot is indicated as (b) (4)

(b) (4), no materials from human or animal origin are used in the manufacture of the AS01 Adjuvant System.

MPL is a purified, non-toxic endotoxin derivative prepared from the lipopolysaccharide of the (b) (4) of *Salmonella minnesota*. (b) (4)

(b) (4)

➤ **Cholesterol**

(b) (4)

➤ **Potassium Dihydrogen Phosphate, Sodium chloride, Disodium phosphate anhydrous, Water for injections**

(b) (4)

3.4.2 (b) (4) EXCIPIENTS, DOPC AND QS-21

3.4.2.1 DOPC

(b) (4) (DOPC) is not described in a (b) (4) . The specifications and analytical procedures are the same as were described in SHINGRIX BLA and are shown in Table 28 and Table 29, respectively.

The Certificate of Analysis for a representative batch of DOPC, batch (b) (4) , is included in the submission and all quality attributes are within acceptance criteria.

Table 28 Specifications for DOPC

(b) (4)

(b) (4)

For DOPC, a description of all analytical methods, including validation of the methods and data to support the quality release acceptance criteria were provided in the BLA were reviewed. These methods were all found to be adequately validated and fit for the purpose of ensuring the quality of the DOPC used in manufacturing.

3.4.2.2 QS-21

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.5 CONTROL OF DRUG PRODUCT

3.5.1 AS01E SPECIFICATIONS, ANALYTICAL PROCEDURES AND RSVpreF3/AS01E FINAL PRODUCT RELEASE SPECIFICATIONS

The specifications for the routine Quality Control (QC) release of the AS01E Final Container are described in GSK (b) (4) sites, respectively. An overview of the QC testing for release of the FC and the list of analytical procedures are summarized in Table 31 and Table 32, respectively.

Table 31 AS01E Final Container release specifications

Tests	Specifications
Description	Opalescent, colorless to pale brownish liquid (b) (4)
(b) (4)	
Volume	(b) (4)
MPL content (b) (4)	
QS-21 content (b) (4)	
(b) (4)	

Tests	Specifications
Cholesterol content (b) (4)	
DOPC content (b) (4)	
(b) (4)	
Sterility test (b) (4)	Absence of growth
Sterility test (b) (4)	Absence of growth

Table 32 Analytical procedures for testing of the AS01E FC

Tests	Reference
Description	In-house
(b) (4)	
Volume	The determination of volume for injection is aligned on the current (b) (4) methods.
MPL content (b) (4)	In-house
QS-21 content (b) (4)	In-house
DOPC content (b) (4)	In-house
Cholesterol content (b) (4)	In-house
(b) (4)	In-house
(b) (4)	In-house
(b) (4)	In-house
(b) (4)	In-house
(b) (4)	In-house
(b) (4)	In-house
(b) (4)	In-house
(b) (4)	In-house
(b) (4)	
Sterility test (b) (4)	

Tests	Reference
Sterility test (b) (4)	

Reviewer: The analytical methods used for release and stability monitoring of AS01E are the same as those used for (b) (4) BLA. A summary of the principles of the in-house analytical procedures is included below.

Summary of the in-house analytical procedures

Description. The product is visually examined for the following characteristics: Presence or absence of particulates, Opalescence, Color, Sedimentation (if applicable)

MPL content (b) (4)

QS-21 content (b) (4)

Cholesterol content (b) (4)

DOPC content (b) (4)

(b) (4)

(b) (4)



(b) (4)



RSVPREF3/AS01E FINAL PRODUCT RELEASE SPECIFICATIONS

The Quality Control for final product, i. e. a packaged box with two vials, RSVPreF3 Lyo and AS01E is performed at (b) (4) facilities. The testing is limited to an identity test to confirm that the

product in the box matches the information on the label. The RSVPreF3E Final Product release specifications for identity include (b) (4) tests:

- Identity of RSVPreF3 (b) (4)

Reviewer: I was not able to locate information on the analytical method (b) (4) for cholesterol content (b) (4), and I was not able to find information on (b) (4) validation for AS01E FC from the manufacturing site (b) (4) for labeling and packaging.

Reviewer: An IR was sent to the company on March 13, 2023 (IR27 Comment 20) to provide the report on the method (b) (4) for cholesterol content (b) (4) (Table 2 in Section 3.2.P.5.1 Specifications RSVPreF3 Lyo, RSVPrF3 Powder Drug Product and Table 1 in Section 3.2.P.3.1 Manufacturers, AS01E Drug Product). The company response was received on March 20, 2023 (see section 2.1 Information Requests, IR10)

Reviewer: IR was sent to the company on March 1, 2023 (IR26, Comment 2) to clarify how AS01E vials are (b) (4) for labelling and packaging and provide a (b) (4) verification study. The company response was received on March 8, 2023 (see section 2.1 Information Requests, IR9).

3.5.2 AS01E BATCH ANALYSIS AND AS01E FC CERTIFICATE OF ANALYSIS

(b) (4)

(b) (4)

(b) (4)

The Certificate of Analysis, AS01E FC

The Certificates of Analysis for the (b) (4) AS01E FC batches (1-dose vials, manufactured at (b) (4) commercial facility and released in 2021), Series (b) (4) batch (b) (4) (b) (4) AS01E batches (b) (4) manufactured at (b) (4) commercial facility and released in 2021 are shown in the BLA (*Section 3.2.R Regional Information*).

3.5.3 AS01E IMPURITIES

Reviewer's note: Potential impurities that may be present in (b) (4) AS01E are the same since (b) (4) adjuvants are similar in composition. A detailed review of product impurities is provided in my review of (b) (4). A summary of the chemical source of impurities and approaches to control for impurities at release and during stability monitoring is included below.

(b) (4)

(b) (4)

3.5.4 AS01E FINAL CONTAINER JUSTIFICATION OF SPECIFICATIONS

The acceptance criteria for AS01E were established in 2015, at the time of the first commercial campaign and it was applied to:

(b) (4)

all AS01E FC (b) (4) 1-dose lots, produced in GMP development facilities and used in clinical trials including RSV OA clinical program.

Sterility tests and (b) (4) measurement applied to AS01E FC are performed according to (b) (4) requirements.

Summary of the Justifications of Specifications for AS01E FC (Section 3.2.P.5.6 in the BLA)

- *Description*; Acceptance criterion: Opalescent, colorless to pale brownish liquid (b) (4)

- *Volume*; Acceptance criterion: (b) (4)
(b) (4)

- *MPL content* (b) (4)

- *QS-21 content* (b) (4)

- *DOPC content* (b) (4)

- *Cholesterol content* (b) (4)

- (b) (4)

(b) (4)

[REDACTED]

- *Sterility test* (b) (4) Acceptance criterion: Absence of growth
Sterility test (b) (4) Acceptance criterion: Absence of growth
Justification: The test is performed according to the (b) (4)

AS01E FC lots used for the determination of specifications are listed. They include clinical lots from (b) (4)

In addition, more recent batches of AS01E manufactured in 2020-2022 were used to support acceptance criteria for AS01E: (b) (4) batches from GMP Developmental Series (b) (4) manufactured at (b) (4), and (b) (4) PPQ Series (b) (4) batches manufactured at (b) (4) were used. The subsequent sections describe the levels of each parameter and illustrate the statistical analysis used to determine acceptance criteria using these reference lots and are acceptable.

Reviewer's assessment: In general, the justification of specifications for AS01E FC are (b) (4)

All justifications are clear and are acceptable.

3.5.5 REFERENCE STANDARDS OR MATERIALS

- For the quantification of MPL, DOPC, and Cholesterol, the company uses reference standards from commercial sources and Certificates of Analysis supplied by the manufacturers.
- For quantification of QS-21, an in-house produced reference standard is used; new reference standards are qualified using pre-established comparability protocols.
- For MPL, QS-21, DOPC, and Cholesterol reference standards, the (b) (4)

2 Pages have been determined to be not releasable: (b)(4)

(b) (4)

3.6 CONTAINER CLOSURE SYSTEM

- AS01E adjuvant is filled in vials sealed with 13 mm stoppers for liquid formulations and secured with flip-off caps. Vial containers, vial stoppers, and vial flip-off caps are received separately; their assembly is carried out during the filling and packaging operations. For each container closure system component, a description and the corresponding specifications are provided in section 3.2.P.7 in the BLA.
- The 3 ml vials are made of type (b) (4) glass, are sterilized by (b) (4), and meet (b) (4) requirements for (b) (4)
- The 13 mm stoppers are made of chlorobutyl rubber, are supplied by (b) (4)
 - The schematic drawing of stoppers is shown in section 3.2.P.7 Container Closure System and is acceptable. The methods and acceptance criteria for 13 mm stoppers are included in Table 2 in the same section. The stoppers are tested for (b) (4)

(b) (4)

- The vial flip-off caps are made of colored polypropylene top fixed on a natural aluminum varnished cap that are not sterilized.
- Information on extractables/leachables study of stoppers, information regarding compatibility between AS01E adjuvant system and container closure, requirement for protection from light, and container closure integrity are summarized in section 2.2.3.7 of this review memo.

3.7 STABILITY

3.7.1 STABILITY SUMMARY AND CLAIMED SHELF-LIFE FOR AS01E

The proposed shelf life for AS01E 1-dose FC lots stored at +2°C to +8°C (equivalent to temperature range describing long-term stability studies temperature, i.e., +5°C ± 3°C) is 36 months from the date of manufacture. The date of manufacture of AS01E DP is defined as the day of start of filling of AS01E Final Container lot.

The stability study of AS01E adjuvant was performed during development and includes data from historical studies and data from batches that were used in Phase 3 clinical trials and commercial batches.

- Stability data included up to (b) (4) -month real-time stability data on GMP development lots and Series (b) (4) and Series (b) (4) commercial campaign batches:

(b) (4)

In these studies, in addition to long-term stability up to (b) (4) months at +5°C ± 3°C, (b) (4) were completed.

All stability data from the (b) (4) -month storage at +5°C ± 3°C studies were within the release acceptance criteria, except for OOS results on (b) (4) due to the presence of (b) (4).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

- *Proposed shelf-life AS01E*

Based on historical data (Stability up to (b) (4) months), product knowledge, stability data available for the GMP development lots (Series (b) (4) 18 months stability), and PPQ lots (Series (b) (4) up to 3 months stability), the company proposes a 36-month shelf life for AS01E 1-dose FC lots stored +2°C to +8°C (equivalent to temperature range describing long-term stability studies temperature, i.e., +5°C ± 3°C) from the date of manufacture .

- *Expiry data for adjuvanted vaccine*

RSV OA vaccine is presented as two independent vials: RSVPreF3 FC and AS01E FC. Therefore, the expiry date of the dual presentation (i.e., the product as packed for sale) is determined by whichever component expires the earliest.

Reviewer's assessments:

The stability data for Series (b) (4) PPQ lots is limited: 1 month and 3 months for batches produced at (b) (4), respectively. The company states that the available stability results "confirm the expected product behavior based on the product knowledge gathered on previous Series". No significant differences were observed between the stability profiles of the PPQ lots and the reference lots at accelerated conditions. No differences in stability under accelerated conditions were observed for lots manufactured at the (b) (4) facilities, confirming comparability of the manufacturing processes between the two sites.

The differences between AS01E FC Series (b) (4) ((b) (4) months stability), Series (b) (4) (18 months stability) and Series (b) (4) PPQ lots are minor: (b) (4). Series (b) (4) AS01E are produced at (b) (4) facility, which is used for series (b) (4) and will be used for commercial production. The differences are in the (b) (4).

The differences between Series (b) (4) AS01E ((b) (4) months stability) and Series (b) (4) (PPQ lots) is (b) (4).

Due to high comparability of the manufacturing processes for which stability data are available for 18 and (b) (4) months and for the current Series C process, for which only 3-months stability are available, I agree with the company's proposed claimed shelf-life of 36 months when stored at 2 to 8 °C.

3.7.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

- *Stability of Series (b) (4) clinical lots*

The stability protocol was provided for ongoing long-term stability studies on Series (b) (4) 1-dose development lots used in clinical studies. The company committed to complete the ongoing long-term stability study (18 months data is already available) according to the stability plan to support the storage of AS01E Adjuvant FC at +5°C ± 3°C for up to (b) (4) months.

The AS01E lots (b) (4) (3-ml 1-dose Type (b) (4) vials closed by butyl rubber stoppers and stored (b) (4)) are being monitored for stability for up to (b) (4) months. The stability studies at accelerated conditions and (b) (4) studies have been completed for Series (b) (4) lots (see section 3.7.1 for summary of the stability)

All analytical attributes that are tested at release are also tested during stability study at all time points including description, (b) (4), QS-21 (b) (4), cholesterol content and DOPC content, (b) (4).

- sterility test is performed at 36 (b) (4) months only.
- CCIT test is performed at 12, 24, 36, (b) (4) months
- Additional characterization tests include (b) (4)

- *Stability of Series (b) (4) PPQ lots manufactured at (b) (4) sites*

Stability study of AS01E Series (b) (4) PPQ lot (b) (4) manufactured at (b) (4) site and stability monitoring of the (b) (4) PPQ Series (b) (4) AS01E lots (b) (4) manufactured at (b) (4) site (3 ml 1-does glass vial stored (b) (4)) will include:

- Long-term stability: $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ for up to (b) (4) months: data collected at T0, and at 3, 6, 9, 12, 18, 24, 36, (b) (4) months. Analytical attributes are assayed as described for Series (b) (4); No characterization tests are planned for Series (b) (4)
- Accelerated stability: (b) (4)

- *Stability monitoring of commercial lots*

For commercial lots, (b) (4) per year and per manufacturing site will be followed for commercial stability for 36 months at $5 \pm 3^{\circ}\text{C}$.

3.8 NONCLINICAL STUDIES

The toxicology studies of RSVPreF3 antigen with and without AS01E adjuvant and of AS01 adjuvant alone (AS01B or AS01E) provided in this submission were reviewed by Dr. Nabil Al Humadi. The studies reviewed by Dr. Al Humadi included Single dose toxicity studies, Repeat dose toxicity studies, Genotoxicity studies, Reproductive and developmental toxicity studies, and Local tolerance studies.


In lieu of Primary Pharmacodynamics studies and Biodistribution studies of AS01E adjuvant, the company provided the reports from studies that were performed with AS01B adjuvant that belong to the same group of AS01 adjuvant systems (as is AS01E) that was historically developed prior to development of the AS01E adjuvant. The nonclinical studies with AS01B or its components (pharmacology and biodistribution) were included in this BLA and were reviewed as part of the SHINGRIX BLA. Since AS01E is very similar by composition and by manufacture to AS01B, this approach is acceptable. In this memo, I provided the list and summaries of the primary pharmacodynamics (section 4.2.1.1 in the submission) and biodistribution (section 4.2.2.3 in the submission) studies that were included in the current BLA STN 12775 and that were previously reviewed for SHINGRIX. This is followed by review of the three Safety and Pharmacology studies (section 4.2.1.3) that were not previously reviewed. These Safety and Pharmacology studies did not identify any cardiovascular or respiratory effects of AS01B in beagle dogs and rats that received AS01B adjuvant at doses equivalent to 7-fold and 140-fold the human dose.

3.8.1 PRIMARY PHARMACOLOGY AND BIODISTRIBUTION STUDIES (PREVIOUSLY REVIEWED FOR SHINGRIX)



Primary Pharmacodynamics studies

1. LIMS20110060-20110061: Contribution of MPL and QS-21 in AS01 effect on antibody and T cell responses
2. LIMS20080769-20080771: Current title: *Impact of (b) (4) changes in the administration of AS01B and gE on innate and gE-specific adaptive immune response in C57BL6 mice* this is the wrong title, should be “Role of (b) (4) in AS01 adjuvant effect” based on the title of the report
3. LIMS20090807-20100654: Impact of (b) (4) injection of AS01B and gE on innate and gE-specific adaptive immune responses in mice.
4. LIMS20110310: Local distribution of AS01B at the injection site administered alone and in combination with the gE antigen
5. LIMS20110226: Characterization of Local innate response induced by AS01
6. LIMS 20110202-20080761 Evaluation of local innate immune response induced by the immune enhancers MPL, QS-21 and their combination in AS01B adjuvant system
7. VR2013QS-21-01: In-vitro characterization of QS-21 ability to activate human immune cells
8. VR2013QS-21-02: In vitro evaluation of molecular pathways of QS-21 interaction with immune cells
9. VR2013QS-21-03: Key role of endocytosis in the immune-stimulatory properties of QS21
10. VR2013MPL01: In vivo deficiency in (b) (4) innate and adaptive response induced by MPL
11. VR2013MPL02: In vitro comparison of MPL and (b) (4) ability to induce (b) (4) cytokines and (b) (4) downstream pathways

(b) (4)




(b) (4)



Biodistribution studies (all were reviewed as part of review of SHINGRIX BLA)

1. (b) (4) : Pilot distribution study of (b) (4) QS-21 following intramuscular administration to (b) (4) Rabbits
2. GSK-CH-01-09: Comparison of the in vivo fate in mice of (b) (4)-DOPC and (b) (4)-QS-21 formulated in AS01B given intramuscularly
3. GSK-CH-01-15: Biodistribution of (b) (4) (in AS01-like formulation) given once intramuscularly in (b) (4) mice
4. (b) (4) -MPL: Pharmacokinetics, distribution, and intravenous administration to the rat
5. (b) (4) -MPL: Pharmacokinetics, distribution and excretion of (b) (4) following intramuscular administration to the rat

(b) (4)




(b) (4)



3.8.2 SAFETY PHARMACOLOGY STUDIES

Study AA81874: AS01B Adjuvant – Effects on cardiovascular and respiratory functions following intramuscular administration in the conscious beagle dog monitored by telemetry.

The aim of the study was to examine the effects of AS01B Adjuvant on arterial blood pressure, heart rate, electrocardiogram, body temperature, and respiratory parameters following a single intramuscular administration in the conscious beagle dog. The study was performed at (b) (4)



The study was performed in general compliance with the Guideline on safety pharmacology studies for human pharmaceuticals (November 2000, issued as CPMP/ICH/539/00 - ICH S7A; published in the Federal Register, Vol. 66, No. 135, July 13, 2001, pages 36791-36792); Guideline on nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals (May 2005, issued as CPMP/ICH/423/02 - ICH S7B; published in the Federal Register, Vol. 70, No. 202, October 20, 2005, pages 61133-61134); EMEA, CPMP/SWP/465/95 December 1997. Note for guidance on preclinical pharmacological and toxicological testing of vaccines, and WHO guidelines on nonclinical evaluation of vaccines, adopted 17-21 November 2003.

Four naïve male beagle dogs, aged 6 to 10 months and weighted 8 to 10 kg, were implanted with telemetry devices (about three weeks prior to the start of dosing). Each animal served as its own control and received the control (saline) and the test item (AS01B, 0.5 ml full human dose) intramuscularly 7

days apart. The selected dose of AS01B represents about 7-fold the human dose based on a 70 kg human. All animals were observed at least twice daily for 14 days. Body temperature, hemodynamic, electrocardiographic, and respiratory parameters were recorded on Day 0 prior to administration, and for 7 days post dose. Serum samples were collected on Days -1, 0, 6 and 7 (the serology data is not shown and is not discussed in the results). The results/conclusion of the study were as follows:

1. AS01B Adjuvant, administered intramuscularly, induced a slight increase in body temperature 6 hours after treatment.
2. AS01B Adjuvant did not affect the arterial blood pressure and the heart rate (including all ECG parameters) during the 72-hour period following administration and did not induce any disturbances in rhythm or waveform morphology of the ECG calculated for the first 6-hour post-treatment period.
3. AS01B Adjuvant did not affect the respiratory rate and the inspiratory and expiratory times.
4. The study concluded that AS01B Adjuvant administered intramuscularly, did not affect the health status and the body weight gain of the animals throughout the study period, induced a slight increase in body temperature 6 hours after treatment, and did not affect the cardiovascular function and the respiratory function.

Study (b) (4) Cardiovascular and Respiratory Evaluations in the Anesthetized rat

The study was performed in accordance with the (b) (4)

(b) (4) adjuvants were administered intravenously at 1 ml/kg dose, which is 140-fold higher dose than the intended human dose. Saline 0.9% w/v was included as a control group and was administered intravenously at 1 ml/kg. Following the induction of surgical anesthesia, cannulations were performed to record cardiovascular (arterial blood pressure, heart rate and ECG) and respiratory parameters. Cardiovascular and respiratory parameters were recorded continuously starting 30 minutes prior to the dose administration and for 120 minutes post-dose. Results and conclusion:

- Intravenous administration of saline, AS01B, AS02B, AS02D, AS02V, AS03A, AS15 and AS25 did not induce any treatment-related effects on any of the recorded cardiovascular or respiratory parameters.
- Values recorded for all cardiovascular and respiratory parameters during prior and post-dose periods were within the normal range expected for this study.
- In conclusion, (b) (4) adjuvants can be considered safe regarding cardio-respiratory side effects as determined by this study.

Study (b) (4) MPL: Cardiovascular and Respiratory Effects in the Anesthetized Dog Following Intravenous Administration

The study was sponsored by the (b) (4)

Four male and four female pure-bred beagle dogs (11 to 13 months of age and weighted 9 to 12 kg) were anesthetized. Vehicle (saline) and test article (MPL) were injected via a cannula placed in the jugular vein. Animals (2 female and 2 male dogs in each group) received three doses of vehicle (1, 1, and 2 ml/kg) in control group or MPL (1, 10, and 100 µg/kg) in test group. Vehicle or test article were administered in ascending doses at intervals of at least 25 minutes. Readings of all hemodynamic and respiratory parameters were taken 10 and 20 minutes before administration of the first dose and at 2, 10, and 20 minutes following the end of infusion of vehicle or MPL. Temperature was monitored with rectal probe; a pulse oximeter was used to monitor the status of the blood oxygen; an intravenous saline-filled cannula was placed in the femoral artery for constant monitoring of blood pressure via a blood pressure transducer; lead II ECG was obtained using subdermal needle electrodes placed in the appropriate positions. Results and conclusion:

In the MPL treated group there was a gradual increase in heart rate over the course of the experiment from a baseline of 83 bpm to 93 bpm by the end of the experiment. This increase was not statistically significant and was observed in a single female dog in the MPL treated group whose heart rate increased from a baseline of 86 bpm to a maximum of 104 bpm by the end of the experiment.

In the MPL treated group in two of the animals, there was a statistically significant dose response for the decrease in the height of the T wave (one of ECG parameters) at 2 minutes after dose administration although there was not a significant difference compared with control group.

An increase in respiratory rate from a baseline mean of 15 brpm (breaths per minute) to 18 brpm, 10 minutes after Dose 3 administration was statistically significant. However, this increase is not great enough to be physiologically relevant.

In conclusion, intravenous administration of MPL at 1, 10 and 100 µg/kg appeared to have little effect on the cardiovascular or respiratory system of a group of anesthetized dogs when compared with a vehicle treated group.