

**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)**

BENEFIT-RISK ASSESSMENT REVIEW MEMORANDUM

March 28, 2023

From: Osman N Yogurtcu, PhD
Senior Staff Fellow
Division of Analytics and Benefit-Risk Assessment
Office of Biostatistics and Pharmacovigilance (OBPV)
CBER, FDA

To: Santosh K Nanda, PhD
Chair of the Review Committee
Office of Vaccines Research and Review (OVRR)

Through: Richard A Forshee, PhD
Deputy Director, OBPV, CBER, FDA

Subject: Benefit-Risk (B-R) BLA Filing Review of STN 125775/0
Respiratory Syncytial Virus Vaccine Recombinant,
Adjuvanted (AREXVY)

Sponsor: GlaxoSmithKline Biologicals SA

Product: Respiratory Syncytial Virus Vaccine Recombinant,
Adjuvanted

Application Type/Number: STN 125775-0004

Proposed Use: Active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus RSV-A and RSV-B subtypes in adults 60 years of age and older

Submission Date: September 2, 2022

Executive Summary. The purpose of this review is to evaluate the BLA submission for AREXVY from a benefit-risk discipline perspective. AREXVY is an Adjuvanted Recombinant Respiratory Syncytial Virus (RSV) Vaccine, sponsored by GlaxoSmithKline Biologicals SA. The vaccine has two components: (1) Recombinant RSV fusion (F) protein RSVPreF3 and (2) proprietary AS01E adjuvant system. The protein sequence of RSVPreF3 is based on contemporary RSV A and RSV B strains. AREXVY is administered as a single-dose intramuscularly. The proposed use of AREXVY is active immunization for the prevention of lower respiratory tract disease (LRTD) caused by RSV-A and RSV-B subtypes in adults 60 years of age (YOA) and older. The submission includes data from a Phase 1/2 clinical study and four pivotal and supportive clinical studies.

This B-R assessment is based primarily on the Sponsor's Global Risk Management Plan (Version 1.0, Section 6) and Clinical Overview (Section 6) documents as well as discussions at the 179th Meeting of Vaccines and Related Biological Products Advisory Committee meeting. Other relevant parts of the submission, including supplementary materials and the Pharmacokinetics and Pharmacology Modules (i.e., M2.6.4 and M2.6.5) were also taken into consideration. Overall, considering the totality of the available evidence, unmet medical need, and outstanding uncertainties, the known and potential benefits of AREXVY administered as a single dose in the target population outweigh the known and potential risks. The FDA's Benefit-Risk Framework for New Drug Review was used to summarize the AREXVY benefit-risk assessment (Table 1, last page).

1. Known and Potential Benefits

Based on Phase 3 clinical trials RSV OA=ADJ-006 and -004, AREXVY have induced robust and persistent humoral and CD4⁺ T-cell immune responses and have provided high and consistent efficacy against RSV disease in the indicated age group for at least one RSV season. The vaccine's efficacy is expected to be higher against more severe outcomes of the RSV disease. The RSV subtype A and subtype B co-circulate, differ regionally, and from year-to-year. The observed efficacy is balanced and similar for both the subtypes. Subgroup analyses of VE do not suggest any meaningful differences by age group, sex, region, hemisphere, race, ethnicity, baseline comorbidity, or frailty status when there were enough participants or cases to conclude. The trial RSV OA=ADJ-007 has shown that AREXVY may be co-administered with a flu vaccine without significant negative impact on the efficacy and safety of the two vaccines. Also, in RSV OA=ADJ-007, lot-to-lot consistency was demonstrated between the three AREXVY lots in terms of RSVPreF3-specific IgG antibody concentration one month after vaccination. Overall, AREXVY has the potential to prevent RSV infection and severe RSV disease in older adults whose treatment would otherwise be limited to supportive care, consisting mainly of supplemental oxygen, intravenous fluids, and bronchodilators.

Effectiveness against RSV-confirmed lower respiratory tract disease (LRTD). The primary endpoint in RSV OA=ADJ-006, the pivotal clinical trial, is to demonstrate the efficacy of AREXVY in the prevention of RSV-confirmed LRTD in the indicated population during the first RSV season. LRTD is defined as physician-assessed two or more lower respiratory symptoms/signs for at least one day. All RSV cases are confirmed by RT-PCR.

The primary endpoint was demonstrated in RSV OA=ADJ-006. The median vaccine efficacy (VE) against the first occurrence of RSV-confirmed LRTD is 82.6%. The lower bound of the 97% CI for VE is 57.9%, much higher than the required 20% threshold. The cumulative incidence curves for RSV-LRTD support a high VE against RSV-LRTD observed through the median follow-up period of 6.7 months, which is longer than the duration of a typical RSV season. We note that the observed median VE against RSV-LRTD is 72.5% for individuals who do not have any pre-existing comorbidities of interest.

Effectiveness against RSV-confirmed acute respiratory infection (ARI). ARI is defined as two or more respiratory symptoms/signs for at least one day, or at least one respiratory symptom/sign and one systemic symptom/sign for at least one day. In RSV OA=ADJ-006, the median vaccine efficacy against the first occurrence of RSV-ARI is 71.7%.

Effectiveness against RSV-associated more severe outcomes. In RSV OA=ADJ-006, severe LRTD is defined as LRTD with at least two LRTD signs or LRTD that is assessed as severe by the responsible investigator. Based on this definition, the median VE is 94.1%. There have been no deaths reported from RSV-confirmed LRTD in the clinical trials.

Effectiveness when co-administered with a quadrivalent inactivated flu vaccine. The trial RSV OA=ADJ-007 has evaluated the immune response, safety, and reactogenicity of AREXVY when co-administered with the Sponsor's FLU-QIV in the indicated population. RSV OA=ADJ-007 demonstrated non-inferior immunogenicity of FLU-QIV and AREXVY co-administration against the sequential administration of each vaccine alone. The non-inferiority criteria dictate that the upper bound of the 95% CI for the flu and RSV GMT ratios (sequential administration group over co-administration group) must be at most 1.5. The results of this trial have the potential to decrease hesitancy to co-administer AREXVY with flu vaccines.

Efficacy in specific subpopulations. Subgroup analyses of VE in RSV OA=ADJ-006 are descriptive, and the study was not powered to demonstrate statistically significant VE in the majority of the subgroups.

Comorbidities and impaired immune functional status. The observed median VE against RSV-LRTD is 94.6% for participants who have at least one pre-existing comorbidity of interest.

Age. The median VE against the first occurrence of RSV-confirmed LRTD in the 60-69 YOA and 70-79 YOA are 81.0% and 93.8%, respectively.

Sex. In RSV OA=ADJ-006, the observed median VE against RSV-LRTD in males is higher (90.5%) than in females (74.1%).

Race and ethnicity. The median VE against RSV-LRTD for white participants and non-Hispanic/Latino participants is 87.2% and 82.1%, respectively, in the RSV OA=ADJ-006 trial.

Regional and hemispheric subgroup analysis. The observed median VEs against RSV-LRTD in North America and Europe are 93.4% and 80.1%, respectively, based on RSV OA=ADJ-006. Also, the observed median VE against RSV-LRTD for only the participants from the northern hemisphere is 82.6%.

Efficacy against RSV-A and RSV-B subtypes. AREXVY provides protection against RSV-confirmed LRTD, irrespective of the predominant circulating subtype during the RSV season. The median VE against RSV-A-LRTD and RSV-B-LRTD are 84.6% and 80.9%, respectively, in the RSV OA=ADJ-006 trial.

Humoral and Cell-mediated Immune Responses. Trial RSV OA=ADJ-004 have evaluated the humoral immune response (i.e., RSV-A/B neutralizing antibody titers and RSVPreF3-specific IgG antibody concentrations), cellular immune response (i.e., RSVPreF3-specific CD4⁺ and CD8⁺ T cell frequencies), and reactogenicity and safety of AREXVY. AREXVY has been demonstrated to be immunogenic in terms of RSV-A and RSV-B NAb titers, RSVPreF3-specific IgG concentrations, and frequency of RSVPreF3-specific CD4⁺ T cells for at least six months after administration as a single dose in adults older than 60 years of age. A waning of humoral and cell-mediated immune responses has been observed for month-six

readouts relative to Day-31 post-administration readouts. No change in the RSVPreF3-specific CD8⁺ T-cell response due to AREXVY was observed at any timepoint.

2. Uncertain Benefits/Data Gaps

There are three challenges because of which the benefits of AREXVY cannot be fully assessed for the indicated population: limited follow-up duration, limited representation from some subpopulations, and lack of some participants due to trial exclusion criteria. Furthermore, there are limited data on the efficacy of AREXVY co-administration with other vaccine types, such as COVID-19, Td/Tdap, and RZV.

There is no established immunologic correlate of RSV protection, and it is currently unknown whether the VE will last longer than one RSV season or if, in the event of waning efficacy, additional doses of AREXVY would be able to maintain protection by boosting the immune response of previously vaccinated individuals. The optimal vaccination interval would then have to be determined. The Sponsor is continuing study RSV OA=ADJ-006 for Season 2 (2022-2023) and the efficacy data are expected to arrive in mid-2023.

Subgroup analyses of VE in RSV OA=ADJ-006 are descriptive, and the trial is not powered to demonstrate statistically significant subgroup VEs:

- Recruiting elderly participants for clinical trials is challenging due to barriers related to exclusion criteria, decreased life expectancy, a lack of commitment or family barriers. In RSV OA=ADJ-006, so far only about a thousand individuals at least 80 years of age have been exposed to AREXVY, and the observed median VE in that subgroup is 34%. This efficacy analysis is inconclusive.
- There are insufficient numbers of RSV-LRTD cases requiring supportive therapy or RSV-related hospitalization to draw any conclusions. Similarly, there were too few RSV-LRTD cases among the frail participants. Frailty was assessed by a gait speed test. We note that only about 1% of the pivotal trial population resides in a long-term care facility.
- Efficacy analysis in RSV OA=ADJ-006 is inconclusive for Hispanic/Latino participants considering that only one RSV-confirmed LRTD case was reported for 1363 participants in this category. Results were also inconclusive in non-white race categories, as there were only two RSV-confirmed LRTD cases in African participants and one in Asian participants.

Additionally, due to the exclusion criteria of the trials, there are no efficacy data on some important subpopulations, such as individuals with:

- Any confirmed or suspected immunosuppressive or immunodeficient condition,
- Any history of dementia,
- Significant underlying illness,
- Serious or unstable chronic illness.

3. Known and Potential Risks

AREXVY has two components: Recombinant RSV fusion (F) protein RSVPreF3 antigen and the AS01_E adjuvant system. Both components are known to induce immune responses in humans. A higher-dose (same-content) adjuvant system (AS01_B) is used in Shingrix, a shingles vaccine already approved by the FDA (since 2017). The pharmacology and toxicity studies performed in mice or rabbits showed that AREXVY is well-tolerated in these animal models and supported its safe use in human subjects. In the Phase 1/2 study RSV OA=ADJ-002, no clinically significant alteration of hematologic or biochemical laboratory parameters was observed following vaccination with AREXVY.

In the four Phase 3 studies, 15,745 participants (the exposed set) from the target population received a single dose of AREXVY with a median follow-up duration of 7.9 months up to a safety data lock point (DLP)

of April 30, 2022. In the December 2022 amendment to the submission, safety data for RSV OA=ADJ-006 (N=12,467) expanded longitudinally. The median follow-up period was extended to 12 months. The identified adverse drug reactions are clinically acceptable for the target population. Subgroup analyses of safety do not suggest any clinically meaningful differences by age group, sex, region, hemisphere, race, ethnicity, baseline comorbidity, or frailty status when there were enough participants or cases to conclude.

There have been no actions taken for safety reasons for AREXVY during its clinical development, including dosage modifications, changes in the target population, formulation changes, restrictions on distribution, or clinical trial suspension. So far, no serious case of hypersensitivity (including anaphylaxis) related to AREXVY within 30 minutes post-vaccination has been reported. Moreover, based on the trial RSV OA=ADJ-007 no safety concerns were identified with the co-administration of AREXVY with FLU-QIV.

Solicited Adverse Events (AEs). In trial RSV OA=ADJ-006, notable adverse events have been administration site and systemic reactogenicity, injection site pain, systemic symptoms (such as myalgia, fatigue, and fever), along with a few solicited Grade 3 adverse events, 4.1% of the vaccinees. Pain has been the most frequent local AE (60.9%) and fatigue has been the most frequent systemic AE (33.6%). The median duration of solicited administration site and systemic events within four days post-vaccination was between one and two days.

Unsolicited AEs. In RSV OA=ADJ-006, the observed incidence of unsolicited AEs within 30 days post-vaccination has been higher in the AREXVY group (33.0%) compared to the placebo group (17.8%). Majority of the unsolicited AEs have been mild to moderate. AREXVY and placebo groups are in general balanced in terms of unsolicited AEs with a medically attended visit within 30 days of vaccination.

Serious and Fatal AEs and Potential Immune-Mediated Disease (pIMD). In RSV OA=ADJ-006, the overall rate of serious AEs, fatal SAEs, and pIMDs are balanced between the vaccine and placebo groups (Figure 1). A higher number of serious and non-serious supraventricular arrhythmic events, primarily events of atrial fibrillation, were reported within 30 days post-vaccination in the RSVPreF3 OA group compared to the placebo group. There was initially a numerical imbalance noted in the events of atrial fibrillation. Of the atrial fibrillation cases that occurred 30 days post-vaccination, 7 events in the RSVPreF3 OA group and 1 event in the placebo group were SAEs (RR: 7.02; 80% CI: 1.47, 75.62). None of these SAEs of atrial fibrillation were considered related to vaccination by the investigator; none resulted in stroke, and none were fatal. We note that the prevalence of atrial fibrillation increases with age (Go et al.). All atrial fibrillation cases occurred in participants with relevant predisposing/concurrent conditions and risk factors. After the safety data update of December 2022, the imbalance has not persisted. Lastly, based on a subgroup analysis in the trial, there have been no observed differences in the frequency of reported fatal SAEs at six months post-vaccination.

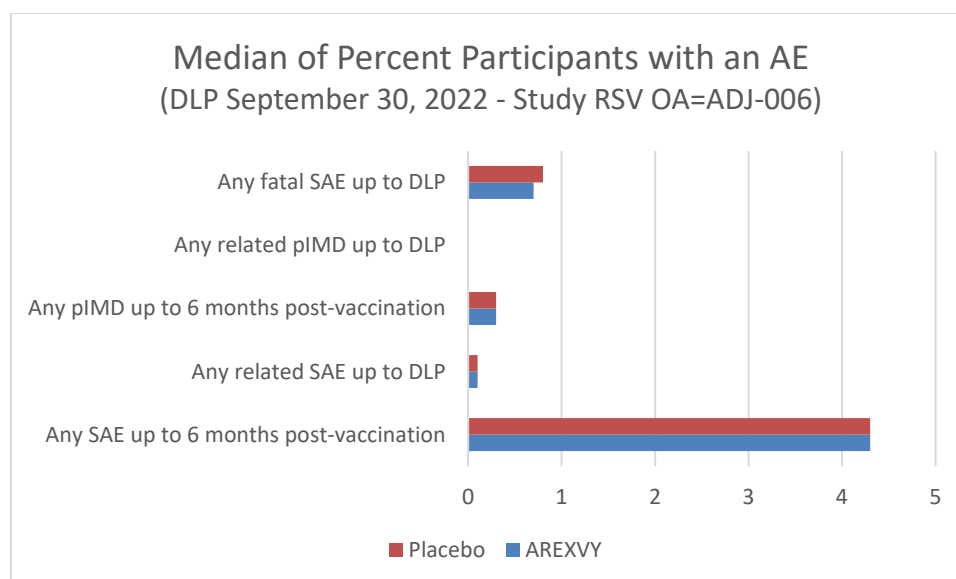


Figure 1. Percentage of the study participants in study RSV OA=ADJ-006 with an AE, DLP September 30, 2022.

There is theoretical concern regarding the exacerbation or triggering of pIMDs linked to the immune-enhancing effects of the AS01 adjuvant [Goud et al.]. Nine out of 15,303 (0.1%) participants in the aggregated safety dataset reported pIMDs that are considered by the investigator to be related to vaccination with AREXVY. Guillain Barré syndrome (GBS) is one of those pIMDs. There have been no cases of GBS observed in the RSV OA=ADJ-006 trial. However, a case of GBS was reported in the revaccination study (RSV OA=ADJ-004) with an onset of nine days after receipt of AREXVY and the case is considered related to vaccination by the FDA. The patient was discharged from hospital six months post-vaccination.

In RSV OA=ADJ-007 (the study on concomitant use with a flu vaccine), there were two acute disseminated encephalomyelitis (ADEM) cases in the co-administration group, one of which was reported as a fatal event. According to the Sponsor, both cases have a level 4 diagnostic certainty based on SPEAC 2021 Brighton Collaboration standards. Level 4 represents a case reported as ADEM but lacking any of the relevant histopathology, clinical characteristics, or imaging to determine an ADEM diagnosis with any certainty.

4. Uncertain Risks/Data Gaps

There are limited data on co-administration safety of AREXVY when administered alongside other vaccine types, such as COVID-19, Td/Tdap, and RZV. Also, due to the exclusion criteria of the trials, there are no safety data on some important subpopulations, such as individuals with:

- Any confirmed or suspected immunosuppressive or immunodeficient condition,
- Any history of dementia,
- Significant underlying illness,
- Serious or unstable chronic illness.

The significance of one GBS case in the safety dataset of about 15,000 exposed individuals is unclear. We note that there is insufficient evidence to confirm that diagnosis (Brighton Level 3 for GBS). A recent self-controlled case series study on US Medicare beneficiaries (age 65 and above) has estimated a median of 3.1 GBS cases per one million doses of an RZV vaccine which uses the same adjuvant as AREXVY [Goud et al.]. On the other hand, population-based rates of GBS increase with age [Sejvar et al.] and RSV infection

has also been associated with GBS in case reports and case series, but a causal link has not been established [Helgeson et al. and Munayco et al.]. We should note that Shingrix has a warning for GBS, with an estimated three excess cases of GBS within the 42 days following million doses administered to adults 65 years or older. The ADEM cases were considered possibly related to either AREXVY or the concomitantly used flu-vaccine.

5. Conclusions Regarding Benefit-Risk

Based on the available evidence, there are more benefits than risks associated with administering a single dose of AREXVY to individuals who are at least 60 years old. RSV is a common cause of respiratory tract disease in older adults, and there are currently no approved treatments. AREXVY has shown through clinical trials to be effective in protecting against RSV-confirmed lower respiratory tract disease for at least one RSV season. Additionally, the level of protection against both RSV subtypes is comparable, and there have been no significant safety concerns raised by trial participant data.

However, there are still some uncertainties regarding the long-term immunogenicity and efficacy of AREXVY, its use in immunocompromised populations, co-administration with relevant vaccines (except the flu vaccine), and the potential for immune-mediated diseases such as GBS and ADEM. To reduce these uncertainties, more research and pharmacovigilance activities will be required. The efficacy study is ongoing with seasons 2 and 3. Also, as of writing of this memorandum, the Sponsor is currently in discussions with the Agency about plans for a postmarketing safety study to evaluate GBS, ADEM, and other immune-mediated demyelinating conditions associated with AREXVY. The discussions are also ongoing regarding determining the inclusion of cardiac disorders as an important potential risk in the pharmacovigilance plan.

6. References

- Ackerson, Bradley, et al. "Severe morbidity and mortality associated with respiratory syncytial virus versus influenza infection in hospitalized older adults." *Clinical Infectious Diseases* 69.2 (2019): 197-203.
- CDC, 2020. RSV in older adults and adults with chronic medical conditions. <https://www.cdc.gov/rsv/high-risk/older-adults.html> (accessed December 2022).
- CDC/RSV-NET. Available at: www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-10-19-20/04-RSV-Adults-Melgar-508.pdf (unpublished, accessed December 2022).
- Go, Alan S., et al. "Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study." *Jama* 285.18 (2001): 2370-2375.
- Goud, Ravi, et al. "Risk of Guillain-Barré syndrome following recombinant zoster vaccine in Medicare beneficiaries." *JAMA Internal Medicine* 181.12 (2021): 1623-1630.
- Hansen, Chelsea L., et al. "Mortality Associated With Influenza and Respiratory Syncytial Virus in the US, 1999-2018." *JAMA network open* 5.2 (2022): e220527-e220527.
- Helgeson, Scott A., Alexander J. Heckman, and Dana M. Harris. "First reported case of respiratory syncytial virus infection causing guillain-Barré syndrome." *Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine* 22.4 (2018): 309.
- McLaughlin, John M., et al. "Rates of Medically Attended RSV Among US Adults: A Systematic Review and Meta-analysis." *Open forum infectious diseases*. Vol. 9. No. 7. Oxford University Press, 2022.
- Munayco, César V., et al. "Large Outbreak of Guillain-Barré Syndrome, Peru, 2019." *Emerging infectious diseases* 26.11 (2020): 2778.
- Sejvar, James J., et al. "Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis." *Neuroepidemiology* 36.2 (2011): 123-133.
- Thompson, William W., et al. "Mortality associated with influenza and respiratory syncytial virus in the United States." *Jama* 289.2 (2003): 179-186.
- Walsh, Edward, et al. "RSV-associated hospitalization in adults in the USA: A retrospective chart review investigating burden, management strategies, and outcomes." *Health science reports* 5.3 (2022): e556.

Table 1 Assessment of AREXVY with the Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> In the US, it is estimated that RSV leads to 60,000-160,000 hospitalizations and 6,000-10,000 deaths annually in the >65 YOA population and the incidence increases with age and comorbidities such as diabetes [CDC/RSV-NET, Hansen et al., Thompson et al., and McLaughlin et al.]. The median length of hospital stay is 3-9 days [Walsh et al.] and observed to be longer than that of influenza-associated hospitalizations [Ackerson et al.]. The COVID-19 pandemic has disrupted RSV's seasonal pattern and RSV-associated hospitalizations were relatively lower for the 2020 and 2021 seasons [CDC/RSV-NET]. There is uncertainty about the future seasonal patterns and RSV incidence. 	<ul style="list-style-type: none"> RSV is a serious disease associated with significant rates of hospitalization, morbidity, and mortality in the target population.
Current Treatment Options	<ul style="list-style-type: none"> No RSV vaccine is currently approved in the US. There are two drugs approved, namely, palivizumab and ribavirin, for infants and young children, but these are not for the BLA's proposed age group. Current treatment of severe RSV disease is limited to supportive care, consisting mainly in supplemental oxygen, intravenous fluids, and bronchodilators. There are RSV vaccine candidates for the prevention of RSV in older adults. 	<ul style="list-style-type: none"> No treatments exist for the RSV-infected individuals in the target population and RSV vaccines may provide important protection against RSV disease.
Benefit	<ul style="list-style-type: none"> AREXVY have induced robust and persistent humoral and CD4⁺ T-cell immune responses and have provided high and consistent efficacy against RSV disease in the indicated age group for at least one RSV season. AREXVY may be co-administered with a flu vaccine without significant negative impact on the efficacy and safety of the two vaccines. Limited follow-up duration, limited or lack of representation from some subpopulations (e.g., Hispanic/Latino). Insufficient numbers of RSV-LRTD cases requiring supportive therapy or RSV-related hospitalization to draw any efficacy conclusions. Lack of data on the efficacy of AREXVY co-administration with other vaccine types, such as COVID-19, Td/Tdap, and RZV. 	<ul style="list-style-type: none"> The totality of the available evidence indicates that single dose of AREXVY has the potential to prevent RSV infection and severe RSV disease in older adults during at least one RSV season. More data and longer follow-up needed to better understand potential immune waning and decreasing vaccine efficacy.
Risk and Risk Management	<ul style="list-style-type: none"> The identified adverse drug reactions are in general clinically acceptable for the target population. The most frequently reported adverse reactions in the Phase 3 trials have been solicited injection site reactions and systemic adverse reactions. Incidence of unsolicited AEs within 30 days post-vaccination is higher in the AREXVY group than the place group, but these AEs have been mild to moderate. Nine out of 15,303 participants in the aggregated safety dataset reported vaccine-related pIMDs. One of those cases was GBS. There was one death due to ADEM considered by FDA as possibly related to flu or AREXVY vaccination. Limited or lack of representation from some subpopulations (e.g., individuals with history of dementia). Lack of data on the safety of AREXVY co-administration with other vaccine types, such as COVID-19, Td/Tdap, and RZV. 	<ul style="list-style-type: none"> The most commonly manifested risks are mild to moderate, self-limited injection site and systemic adverse reactions. pIMDs are less commonly manifested but constitute a potentially serious risk. Post-deployment monitoring for adverse events using both passive and active surveillance systems will be needed to assess and quantify emerging safety concerns.