# VLA-401: JE-VC post-marketing adverse event surveillance among U.S. military personnel

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# 401 Safety Surveillance Study

## Active Surveillance for Adverse Events after Immunization with IXIARO among U.S. Military Service Personnel

**Primary Objective:**

+ To detect, verify and characterize rare, potentially serious adverse events (SAEs) such as neurological or hypersensitivity reactions among 20,000 IXIARO vaccinated military personnel.

**Secondary Objectives:**

+ To identify unexpected or unanticipated adverse events that are possibly associated with IXIARO vaccination by performing data mining for events with significantly higher incidence after IXIARO vaccination than in an IXIARO non-exposed comparison group of JE-VAX vaccinees. Among these, to identify medically significant events (i.e. two outpatient visits or one inpatient visit within 7 days after vaccination).

# 401 Safety Surveillance Study - Analysis population

Defense Medical Surveillance System (DMSS) database
**Male and female active duty US military personnel (Army, Navy, Air Force and Marines)**
≥17 years of age who received at least one dose of either IXIARO or JE-VAX

21,347 subjects vaccinated with IXIARO between 01 Jul 2010 – 27 May 2011
49 441 subjects vaccinated with JE-VAX between 01 Jan 2009 – 27 May 2011

**Tier 1 events**

List of pre-defined, serious ICD-9 codes potentially associated with vaccines

**Tier 2 events**

ICD-9 codes detected with case N≥5 and significantly increased IR in IXIARO group
and
Two outpatient visits or a hospitalization within 7 days after the primary ICD9 code reporting date

# 401 Safety Surveillance – All subjects in the Tier 1 Analysis

## Description of Study Population, DMSS Database

| | JE-VAX | | IXIARO | |
|---|---|---|---|---|
| | **N** | **%** | **N** | **%** |
| **Total subjects** | **49,441** | 100 | **21,347** | 100 |
| Total doses | 101,957 | | 36,358 | |
| **Age** | | | | |
| Mean age | 26.8 years | | 24.9 years | |
| ≤24 | 24,118 | 49% | 13,039 | 61% |
| 25-34 | 17,549 | 35% | 6,433 | 30% |
| ≥35 | 7,774 | 16% | 1,875 | 9% |
| **Sex** | | | | |
| Female | 3,741 | 8% | 1,524 | 7% |
| Male | 45,700 | 92% | 19,823 | 93% |

# Tier 1 events

# 401 Safety Surveillance Study - Analysis population

**21,347 subjects vaccinated with IXIARO**
49 441 subjects vaccinated with JE-VAX

↓

Active electronic surveillance for ICD-9 CM coded AEs within 42 days after each vaccination

↓

**Tier 1 events**

**182** subjects with predefined Tier 1 ICD9-codes detected
**4** subjects excluded as non-eligible
**5** subjects could not clearly be assigned to either IXIARO or JE-VAX

**45** subjects assignable to IXIARO and
**128** subjects assignable to JE-VAX
included in the IRR analysis of Tier 1 events

↓

Detailed study of Electronic Health Records including verification of diagnosis, temporal association with vaccination, medical history, concomitant medications and outcome of events and transfer of information into individual Case Report Forms (CFRs)

↓

**Tier 1 events – IXIARO Eligible Population**

**2** subjects could be assigned to IXIARO upon CRF review
**1** subject considered non-eligible, as notes on CRF confirmed that Tier 1 event already occurred 4 months before documented visit

**46** subjects subjects assignable to IXIARO included in the
Eligible Population for assessment of causal relationship with IXIARO by an independent Data safety monitoring board (DSMB)

# 401 Safety Surveillance Study – Tier 1 AE incidence rates & ratios

## DMSS Database

| | JE-VAX | | | IXIARO | | | | |
|---|---|---|---|---|---|---|---|---|
| **Tier 1 AE** | **Case N** | **Person Year** | **IR per 1000 py** | **Case N** | **Person Year** | **IR per 1000 py** | **IRR** | **P-value** |
| Ataxia | 1 | 9206 | 0.11 | 0 | 3634 | 0 | 0 | 1 |
| Bell's Palsy | 3 | 9193 | 0.33 | 0 | 3632 | 0 | 0 | 1 |
| Bronchospasm | 2 | 9191 | 0.22 | 0 | 3628 | 0 | 0 | 1 |
| Cerebrovascular accident | 0 | 9210 | 0 | 0 | 3637 | 0 | . | 1 |
| CNS Inflammation / Encephalitis | 1 | 9205 | 0.11 | 0 | 3636 | 0 | 0 | 1 |
| Encephalopathy | 1 | 9208 | 0.11 | 0 | 3635 | 0 | 0 | 1 |
| Guillain-Barré-Snydrome | 0 | 9209 | 0 | 0 | 3637 | 0 | . | 1 |
| Multiple sclerosis | 0 | 9207 | 0 | 0 | 3636 | 0 | . | 1 |
| Myelitis | 1 | 9205 | 0.11 | 0 | 3636 | 0 | 0 | 1 |
| Neuropathy | 4 | 9195 | 0.44 | 0 | 3633 | 0 | 0 | 1 |
| TIA | 1 | 9204 | 0.11 | 0 | 3635 | 0 | 0 | 1 |
| ADEM | 0 | 9211 | 0 | 0 | 3637 | 0 | . | 1 |

# 401 Safety Surveillance Study – Tier 1 AE incidence rates & ratios

## DMSS Database

| | JE-VAX | | | IXIARO | | | | |
|---|---|---|---|---|---|---|---|---|
| **Tier 1 AE** | **Case N** | **Person Year** | **IR per 1000 py** | **Case N** | **Person Year** | **IR per 1000 py** | **IRR** | **P-value** |
| **Convulsion** | 9 | 9185 | 0.98 | **6** | 3627 | 1.65 | 1.69 | 0.27 |
| **Delayed hypersensitivity / Serum sickness[a]** | 5 | 9205 | 0.54 | **3[a]** | 3635 | 0.83 | 1.52 | 0.58 |
| **Anaphylactic shock** | 7 | 9188 | 0.76 | **2** | 3629 | 0.55 | 0.72 | 0.75 |
| **Angioedema[a]** | 6 | 9183 | 0.65 | **2[a]** | 3629 | 0.55 | 0.84 | 0.96 |
| Neuritis | 84 | 8845 | 9.5 | 29 | 3525 | 8.23 | 0.87 | 0.84 |
| Meningitis | 1 | 9198 | 0.11 | 2 | 3634 | 0.55 | 5.06 | 0.23 |
| *Ptosis[c]* | *2* | *9200* | *0.22* | *1[c]* | *3632* | *0.28* | *1.27* | *0.83* |

[a] Single additional subject assigned to IXIARO group after CRF review as documented JE-VAX vaccination was outside of the time window of 42 days after diagnosis of Tier One code.
[c]considered non-eligible, as notes on the (CRF) revealed that the Tier One event had already occurred 4 months before the documented visit date, hence an exclusion criterion was met.

## 401 Safety Surveillance

# Electronic Health Records - Convulsion

| Subject | Description | Time post vaccination | Concurrent vaccines | Causality specified | If applicable: Further dose IXIARO given after recorded event |
|---|---|---|---|---|---|
| 10005 | Code 780.39, Other convulsions | Onset three weeks prior to and 5 weeks after first IXIARO vaccination | Rabies Vaccine | No | Second and third IXIARO dose given |
| 10009 | Code 780.39, Other convulsions | Onset 5 days after first IXIARO vaccination | Influenza Vaccine | No | Second IXIARO dose given |
| 10010 | Code 780.39, Other convulsions | Onset 1 month after first IXIARO vaccination | Tyhpoid Vaccine | No | Second IXIARO dose given |
| 10012 | Code 780.39, Other convulsions | Onset 21 days after IXIARO vaccination | - | No | - |
| 10050 | Code 780.39, Other convulsions | Onset 4 days after second IXIARO vaccination | Smallpox and anthrax vaccinations | No | - |
| 10011 | Code 345.9 Epilepsy, unspecified | Onset approx. 5.5 weeks after second IXIARO vaccination | - | No | - |

## 401 Safety Surveillance

# Electronic Health Records – Delayed hypersensitivity / Serum sickness

| Subject | Description | Time post vaccination | Concurrent vaccines | Causality specified | If applicable: Further dose IXIARO given after recorded event |
|---|---|---|---|---|---|
| 10004 | Code 999.5, Other serum reaction | Onset on day of IXIARO vaccination | - | No | - |
| 10016 | Code 999.5, Other serum reaction | Onset 1 week after first IXIARO vaccination | Anthrax given concomitantly | Yes | Second IXIARO dose given |
| 10019 | Code 999.5, Other serum reaction | Onset 1 month after first IXIARO vaccination | Anthrax given concomitantly | No | Second IXIARO vaccination given 2 days after event |
| 10012 | Code 999.5, Other serum reaction | Onset on day of first IXIARO vaccination | - | No | Second IXIARO dose given |

## 401 Safety Surveillance

# Electronic Health Records - Anaphylactic shock

| Subject | Description | Time post vaccination | Concurrent vaccines | Causality specified | If applicable: Further dose IXIARO given after recorded event |
|---|---|---|---|---|---|
| 10008 | Code 999.4, Anaphylactic shock due to serum | Onset 21 days after second IXIARO vaccination | Anthrax given concomitantly | No | - |
| 10013 | Code 999.5, Other anaphylactic shock | Event onset 2 months after 1st and 3 days before 2nd IXIARO vaccination | - | No | - |

Patient presented in an emergency department 2 months after 1st IXIARO vaccination with dermatitis, in particular full body rash, itchy, and shortness of breath.
Patient denied taking new foods, soaps or detergents
Patient was prescribed prednisone, benadryl (diphenhydramine) and zantac (ranitidine). Diagnosis of anaphylaxis was made.

## 401 Safety Surveillance

# Electronic Health Records – Angioedema

| Subject | Description | Time post vaccination | Concurrent vaccines | Causality specified | If applicable: Further dose IXIARO given after recorded event |
|---|---|---|---|---|---|
| 10031 | Code 995.1, Angioneurotic edema, not elsewhere classified | Onset 15 days after 2nd IXIARO vaccination | Rabies vaccination given concomitantly | No | - |
| 10044 | Code 995.1, Angioneurotic edema, not elsewhere classified | Onset 25 days after first IXIARO vaccination | - | Yes (Bee sting) | Second IXIARO dose given |
| 10001 | Code 995.1, Angioneurotic edema, not elsewhere classified | Onset 2 weeks after first IXIARO vaccination | - | No | Second IXIARO vaccination given |

# 401 Safety Surveillance Study – Eligible Tier 1 Population

## At least one AE which was assessed 'possibly related' by DSMB by ICD-9 CM Code

| ICD-9 CM Code | Medical Term / Diagnosis | Total (N=46) No. (%)* |
|---|---|---|
| 723.4 | Brachial neuritis or radiculitis NOS | 4 (8.7) |
| 780.39 | Other convulsions | 2 (4.3) |
| 999.5 | Other serum reaction not elsewhere classified | 3 (6.5) |
| 999.4 | Anaphylactic reaction to serum | 1 (2.2) |
| 995.1 | Angioneurotic edema, not elsewhere classified | 2 (4.3) |
| **Total number of subjects with AEs assessed as related** | | **12 (26.1)** |
| Total number of such AEs | | 17 |

Subjects are counted only once per ICD-9 CM Code
* Percentages are based on N

# Tier 2 events

# 401 Safety Surveillance Study –Tier 2 event counts via DMSS

## All ICD-9 Codes with Case N≥5 and significant Incidence Rates Ratio

| | | JE-VAX | | | IXIARO | | | Crude IRR (Ixiaro vs Je-Vax) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **ICD-9** | **Description** | **Case N** | **Person Year** | **IR per 1000 py** | **Case N** | **Person Year** | **IR per 1000 py** | **IRR** | **Lower 95% CI** | **Upper 95% CI** | **P-value** |
| 0229 | Anthrax unspecified | 9 | 9210 | 0.98 | 38 | 3632 | 10.46 | 10.71 | 5.18 | 22.14 | <.0001 |
| 470* | Deviated nasal septum | 21 | 9209 | 2.28 | 15 | 3635 | 4.13 | 1.81 | 0.93 | 3.51 | 0.0358 |
| **Total** | | **30** | | | **53** | | | | | | |

# Conclusions

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# 401 Safety Surveillance Study
## Conclusions

+ In a population of 21,347 US military personnel receiving 36, 358 doses of IXIARO, screening for pre-defined events (i.e. AEs with evidence or suspicion of an association with JE vaccines or excipients and adjuvants) revealed no statistically significant increased Incidence Rates (IR), compared to a reference population of subjects vaccinated with JE-VAX (N= 49 441).
+ Data mining for non-predefined events with statistically significant higher IR in the IXIARO population compared to the JE-VAX population revealed no events with causal relationship for vaccination with IXIARO.
+ No safety signals have been identified during the review of the 401 study data.
+ Overall, this review of data on more than 20.000 military personnel vaccinated with IXIARO strengthened IXIARO's good safety profile known from clinical development as well as from post-marketing experience since 2009.
+ The benefit-risk evaluation for IXIARO remains positive and unchanged compared to that at time of authorisation.

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