Duration of Protection After Primary Series and Booster Dose of IXIARO

Background and Introduction

+ IXIARO primary series was approved by FDA in 2009 for use in persons 17 years of age and older

+ Initial data on antibody persistence after a primary series of IXIARO, the immunogenicity and safety of a booster dose, and duration of protection after the booster were added to the IXIARO prescribing information in 2010

+ The data were presented to ACIP and a booster recommendation was issued in 2011*

+ In 2013, the IXIARO primary series indication was expanded to include children from 2 months of age; and ACIP issued a respective recommendation:
  › Data on need for and timing of a booster in children were not available at the time

New clinical data are now available on duration of protection after primary series and after a booster dose, both in adults and in children

*MMWR / May 27, 2011 / Vol. 60 / No. 20
Presentation Topics

IXIARO Clinical Data in Adults:
1. Duration of protection following the primary series
2. Duration of protection following a booster dose
3. Regulatory Status: Booster dose recommendations

IXIARO Clinical Data in Children:
1. Duration of protection following the primary series
2. Duration of protection following a booster dose
3. Regulatory Status: Booster dose recommendations
Duration of Protection After Primary Series and Booster Dose of IXIARO
Overview of Clinical Data in Adults

+ Three clinical trials in adults provide data relevant to persistence of antibodies
+ New clinical data for IXIARO are available for both antibody persistence after primary series and after booster dose
  › Today’s presentation provides a comprehensive summary of available clinical data (both old and new)

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-Up After Primary Series (Reviewed by ACIP)</th>
<th>Follow-Up After Primary Series (New Data)</th>
<th>Follow-Up After Booster (Reviewed by ACIP)</th>
<th>Follow-Up After Booster (New Data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC51-303</td>
<td>36 months</td>
<td>60 months</td>
<td>Not Done</td>
<td></td>
</tr>
<tr>
<td>IC51-311</td>
<td>15 months</td>
<td></td>
<td>12 months (all subjects)</td>
<td>76 months (subgroup)</td>
</tr>
<tr>
<td>IC51-305</td>
<td>24 months</td>
<td></td>
<td>13 months</td>
<td></td>
</tr>
</tbody>
</table>
## Long-Term Immunogenicity Study
### Study Design for Trial IC51-303

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Long-term Immunogenicity and Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Population</td>
<td>181 Subjects ≥18 years of age, vaccinated in previous studies (Days 0 and 28)</td>
</tr>
<tr>
<td>Design</td>
<td>Single-arm, Phase 3 Follow-up Study</td>
</tr>
<tr>
<td>Treatment Groups</td>
<td>No treatment administered</td>
</tr>
<tr>
<td></td>
<td>N=181 (up to Month 24) N=152 (up to Month 60)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2, 6, 12, 24, 36, 48 and 60 months after the first vaccination</td>
</tr>
<tr>
<td>Countries / Sites</td>
<td>4 study sites in Austria, Germany and Romania</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Primary EP: SCR at Month 24 after first vaccination</td>
</tr>
<tr>
<td></td>
<td>Secondary EPs: GMT at Month 24 after first vaccination</td>
</tr>
<tr>
<td></td>
<td>Immunogenicity (SCR and GMT) at Months 2, 6, 12, 36, 48 and 60</td>
</tr>
<tr>
<td></td>
<td>Rate of subjects with SAEs and medically attended AEs up to Month 6</td>
</tr>
<tr>
<td></td>
<td>Unsolicited Adverse Events</td>
</tr>
</tbody>
</table>

24 February 2016
Long-Term Immunogenicity Study, IC51-303
Seroprotection Rate and Geometric Mean Titer up to Month 60

- SPR (rate of subjects with a protective titer, PRNT$_{50}$ ≥1:10) decreased in the first year, then remained stable at approximately 80% up to 5 years
- GMT decreased markedly in the first year, then remained stable at a GMT of approximately 40 for up to 5 years

Long-Term Immunogenicity Study, IC51-303
Post-hoc Analysis: Impact of TBE Vaccination on SPR

+ Subjects were grouped by their Tick-Borne Encephalitis virus vaccination status at each study visit:
  › No TBE vaccination up to the specific time point
  › TBE vaccination prior to first dose of IXIARO, but no TBE vaccination during the study
  › TBE vaccination during the study (after IXIARO vaccination)

+ TBE-vaccine exposure (prior and concomitant TBE vaccination) seems to positively influence antibody persistence

<table>
<thead>
<tr>
<th>Months After Primary Vaccination</th>
<th>Seroprotection Rate [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>N= 93 87</td>
</tr>
<tr>
<td>6</td>
<td>N= 92 83 6</td>
</tr>
<tr>
<td>12</td>
<td>N= 92 81 8</td>
</tr>
<tr>
<td>24</td>
<td>N= 78 68 18</td>
</tr>
<tr>
<td>36</td>
<td>N= 57 56 28</td>
</tr>
<tr>
<td>48</td>
<td>N= 55 52 29</td>
</tr>
<tr>
<td>60</td>
<td>N= 47 42 36</td>
</tr>
</tbody>
</table>

# indicates non-overlapping 95%CI's for groups “TBE Vaccination During Study” and “No TBE Vac”

1 Dubischar-Kastner et al. Abstract LB-2357; American Society of Tropical Medicine and Hygiene 2011
## IXIARO Main Booster Trial

### Study Design for Trial IC51-311

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Effect of a Booster Dose on Long-term Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Population</td>
<td>198 Subjects ≥18 Years of Age</td>
</tr>
<tr>
<td>Design</td>
<td>Single-Arm, Open-Label Follow-Up Study</td>
</tr>
<tr>
<td>Treatment Group</td>
<td>IXIARO Booster 0.5 ml, i.m. at Month 15 after Primary Immunization, N = 198</td>
</tr>
<tr>
<td>Follow-up</td>
<td>1, 6 and 12 Months after the Booster</td>
</tr>
<tr>
<td>Countries / Sites</td>
<td>3 Study Sites in Austria and Germany</td>
</tr>
</tbody>
</table>
| Endpoints           | Primary EP: SCR at Month 12 after the booster vaccination  
                      Main Secondary EPs:  
                      SCR at Day 28 and Month 6 after the booster vaccination  
                      GMT at Day 28, Month 6 and Month 12  
                      Solicited and Unsolicited AEs up to Month 12 |
IXIARO Main Booster Trial, IC51-311
SPR+ and GMT at Day 56 and Month 15 after Primary Series (Pre-Booster)

+ In this trial, SPR dropped to 69% by 15 Months after start of the primary series
  › GMT after primary immunization was lower compared to long-term immunogenicity study, IC51-303

Eder et al, Long term immunity following a booster dose of the inactivated Japanese Encephalitis vaccine IXIARO®, IC51. Vaccine 2011,29;2607–2612
## Supportive Booster / Long-term Immunogenicity Study

### Study Design for Trial IC51-305

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Long-term immunogenicity; Response to booster dose in subjects without measurable antibody titers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Population</td>
<td>356 subjects ≥18 years of age who received one of three different doses / schedules of IXIARO in a preceding trial. Only data for standard schedule group shown here</td>
</tr>
<tr>
<td>Design</td>
<td>Open-Label, Phase 3 Follow-up Study</td>
</tr>
<tr>
<td>Treatment Group</td>
<td>Booster for seronegative subjects only: 0.5 mL IXIARO. -Subjects seronegative at Month 6 boosted at Month 11 -Subjects seronegative at Month 12 boosted at Month 23</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2 years after primary series. Up to 12 months after booster</td>
</tr>
<tr>
<td>Countries / Sites</td>
<td>2 study sites in Germany and Northern Ireland</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Primary EP: SPRs at Month 24 (Seronegative subjects received a booster but remained classified as seronegative for subsequent time points in this analysis). Main Secondary EPs: SPRs at Month 6, 12 and 24 GMTs at Month 6, 12, 24 SAEs and medically attended AEs, local and systemic tolerability of booster</td>
</tr>
</tbody>
</table>
Supportive Booster / Long-term Immunogenicity Study, IC51-305
Antibody Persistence Without Booster

+ In this trial, SPR dropped to 58% by 12 Months after start of the primary series
+ Serology at Month 6, 12 and 24 after the primary series
  › Seronegative subjects received a booster per study protocol, but remained classified as seronegative for subsequent time points in this analysis
Presentation Topics

IXIARO Clinical Data in Adults:
1. Duration of protection following the primary series
2. Duration of protection following a booster dose
3. Regulatory Status: Booster dose recommendations

IXIARO Clinical Data in Children:
1. Duration of protection following the primary series
2. Duration of protection following a booster dose
3. Regulatory Status: Booster dose recommendations
A booster dose at 15 months after primary vaccination generated 100% seroprotection.

- SPR remained at 99% 12 months after the booster dose.
- Titers remained higher than after primary series for at least one year after booster.
6-Years Extension Trial to IXIARO Main Booster Trial
Neutralizing Antibodies 6 Years After Booster in a Subset of the Original Study Population (Investigator-Sponsored Study)¹

+ 67 / 198 subjects from main booster trial were available for serological sampling
+ Average time from IXIARO booster: 76 months
  › SPR remained at 96% approximately 6 years after booster dose

¹ PRNT assay conducted by Valneva
Paulke-Korinek et al, Persistence of Antibodies Six Years after Booster Vaccination with Inactivated Vaccine against Japanese Encephalitis. Vaccine 2015
6-Years Extension Trial to IXIARO Main Booster Trial
Modeled Duration of Protection after 1st IXIARO Booster

Mathematical modeling (log-linear model*) was applied to further predict antibody decline and duration of protection.

- PRNT$_{50}$ titer of 1:10 was defined as limit for protection.
  - Duration of protection depends on titer level after booster.
  - Estimated 75% of subjects will be protected for a minimum of 10 years.
  - Average duration of protection is projected to be 14 years, range 2-25 years.

Authors concluded further booster doses should be scheduled after 10 years.
Safety/efficacy of a 2nd booster or need for a 2nd booster has not been approved by FDA.

* Model uses a log-linear antibody decline with a structural break at month6, based on individual subject titer kinetics
Paulke-Korinek et al, Persistence of Antibodies Six Years after Booster Vaccination with Inactivated Vaccine against Japanese Encephalitis. Vaccine 2015
Summary and Conclusions

+ Based on waning neutralizing antibody titers (SPR range 83% to 58%), a booster of IXIARO should be considered / recommended at 12 months after the primary series

+ Clinical data demonstrate a booster dose of IXIARO will elicit a memory response at least until 23 months after the primary series*

+ After an IXIARO booster dose, clinical data demonstrate high levels of seroprotection for 6 years

+ Mathematical modelling suggests seroprotection may persist for at least 10 years after the booster dose of IXIARO in 75% of vaccinees

+ Safety data for a booster dose of IXIARO were presented to ACIP for the booster recommendation vote in 2011. No safety concerns were identified and the AE profile was in-line with the primary series*

* In the interest of time, these data on a booster dose of IXIARO in adults are not re-presented in this presentation, but are described in the Prescribing Information for IXIARO
Presentation Topics

IXIARO Clinical Data in Adults:
1. Duration of protection following the primary series
2. Duration of protection following a booster dose
3. Regulatory Status: Booster dose recommendations

IXIARO Clinical Data in Children:
1. Duration of protection following the primary series
2. Duration of protection following a booster dose
3. Regulatory Status: Booster dose recommendations
IXIARO Booster Dose Recommendation in Adults

Regulatory Status and Outlook

+ In Europe, the Summary of Product Characteristics gives clear guidance for healthcare professionals for the first booster dose:

“A booster dose (third dose) should be given within the second year (i.e. 12 - 24 months) after primary immunization, prior to potential re-exposure to JEV. Persons at continuous risk for acquiring Japanese encephalitis (laboratory personnel or persons residing in endemic areas) should receive a booster dose at month 12 after primary immunization.”

› A recommendation for a second booster dose after 10 years is currently under review.

+ In the United States, both the Prescribing Information and the ACIP recommendations use less prescriptive language than Europe for first booster dose:

“Individuals 17 years of age and older: If the primary series of two doses was completed more than 1 year previously, a booster dose may be given if ongoing exposure or re-exposure to JEV is expected.”

› FDA indicated that without actual safety / immunogenicity data (instead of mathematical modeling), no recommendation for a second booster would be granted. Valneva has no current plans to submit additional antibody persistence data for IXIARO to FDA.
Presentation Topics

IXIARO Clinical Data in Adults:
1. Duration of protection following the primary series
2. Duration of protection following a booster dose
3. Regulatory Status: Booster dose recommendations

IXIARO Clinical Data in Children:
1. Duration of protection following the primary series
2. Duration of protection following a booster dose
3. Regulatory Status: Booster dose recommendations
Duration of Protection After Primary Series and Booster Dose of IXIARO
Overview of Clinical Data in Children

+ Two clinical trials in children provide data relevant to persistence of antibodies
+ One clinical trial provides data on antibody persistence after booster dose
  › Today’s presentation provides a comprehensive summary of available clinical data on primary series and booster

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Duration of Follow-Up Initial Study*</th>
<th>Duration of Follow-Up Extension Study*</th>
<th>Follow-Up After Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC51-322 / IC51-324</td>
<td>JE Non-Endemic</td>
<td>7 months</td>
<td>36 months (subgroup)</td>
<td>None administered</td>
</tr>
<tr>
<td>IC51-323 / IC51-325</td>
<td>JE Endemic</td>
<td>7 months</td>
<td>36 months (subgroup)</td>
<td>24 months (subgroup), booster given at month 12</td>
</tr>
</tbody>
</table>

* Duration of follow-up calculated from administration of the first dose of the primary series
# IXIARO Trial in Traveling Children

## Study Design for Trial IC51-322 / IC51-324

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Safety and Immunogenicity of IXIARO in a JEV Naïve, Pediatric Travelers Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Population</td>
<td>Children and adolescents, ≥2 months to &lt;18 years</td>
</tr>
<tr>
<td>Design</td>
<td>Open-label, single-arm trial with an extension study:</td>
</tr>
<tr>
<td></td>
<td>100 children evaluated for safety</td>
</tr>
<tr>
<td></td>
<td>64 children evaluated for immunogenicity</td>
</tr>
<tr>
<td></td>
<td>23 children enrolled in extension study IC51-324</td>
</tr>
<tr>
<td>Treatment Groups</td>
<td>&lt;3 years of age: 0.25 mL IXIARO, N = 12</td>
</tr>
<tr>
<td></td>
<td>3 years to &lt;18 years of age: 0.5 mL IXIARO, N = 88</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Day 56 and Month 7 in parent study, Month 12, 24 and 36 in extension trial</td>
</tr>
<tr>
<td>Countries / Sites</td>
<td>15 Study sites in Australia, Germany, USA, Denmark, Sweden</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Parent Study Primary Endpoint:</td>
</tr>
<tr>
<td></td>
<td>Rate of SAE/ Medically-attended AEs until Day 56</td>
</tr>
<tr>
<td></td>
<td>Secondary Endpoints:</td>
</tr>
<tr>
<td></td>
<td>Immunogenicity (SCR/ GMT) up to Month 36</td>
</tr>
</tbody>
</table>

Dubischar-Kastner et al., Abstract P 2.7, 5th Northern European Conference on Travel Medicine, June 5-8 2014 Bergen, Norway
Dubischar-Kastner et al., Abstract FC2.04, Presented at the 14th Conference of the International Society of Travel Medicine, May 25-28 2015, Quebec, Canada
Long-term data are limited in traveling children, due to recruitment issues.

In children aged ≥3 years at primary immunization, SPR decreased in the first 6 months, then remained stable at approximately 90% up to 3 years.

One child <3 years enrolled in the extension study, and retained a protective titer.
# IXIARO Antibody Persistence / Booster in Philippine Children

## Study Design for Trial IC51-325

<table>
<thead>
<tr>
<th><strong>Objectives</strong></th>
<th>Long-term Persistence of Immunity and Safety and Immunogenicity of a IXIARO Booster Dose in Children from JE endemic regions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Population</strong></td>
<td>300 children / adolescents aged 2 months – 17 years, vaccinated in preceding trial in endemic region</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Open-label, Randomized, Phase 3 Study</td>
</tr>
</tbody>
</table>
| **Treatment Groups** | Randomized 1:1 into Booster Group (12 months after first vaccination) and Non-Booster Group  
IXIARO Booster Group, N=150: IXIARO 0.25 mL, <3 years, N=81; 0.5 mL, ≥3 years, N=67  
Non-booster Group, N = 150 |
| **Follow-up** | Month 13 after first immunization (i.e., 4 weeks after booster dose) and Month 24 for Safety and Immunogenicity |
| **Countries / Sites** | 3 study sites in the Philippines |
| **Endpoints** | Primary Endpoint: SCRs* at 1 month after the booster dose  
Main Secondary Endpoints:  
GMTs# at 1 month after the booster dose  
SAEs and medically attended AEs following 1 month after the booster dose |

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Dubischar-Kastner et al., Abstract P 2.8, 5th Northern European Conference on Travel Medicine, June 5-8 2014 Bergen, Norway  
Dubischar-Kastner et al., Abstract FC2.04, Presented at the 14th Conference of the International Society of Travel Medicine, May 25-28 2015, Quebec, Canada  
IXIARO Update for ACIP  
24 February 2016
IXIARO Antibody Persistence in Philippine Children
Seroprotection Rate and Geometric Mean Titer up to Month 36

+ 149 children were followed for maximum 3 years, mean age 4.6 years at primary
+ SPR decreased in the first 6 months, then remained stable at approximately 90% up to 3 years (combined data for all ages / doses)
+ Titer increases suggestive of natural JEV exposure were observed in 24/150 children during follow-up
Age groups 1 - <3 years and 3 - <12 years showed stronger decline in protection rate down to ~80% at Month 7.
Presentation Topics

IXIARO Clinical Data in Adults:
1. Duration of protection following the primary series
2. Duration of protection following a booster dose
3. Regulatory Status: Booster dose recommendations

IXIARO Clinical Data in Children:
1. Duration of protection following the primary series
2. Duration of protection following a booster dose
3. Regulatory Status: Booster dose recommendations
IXIARO Booster in Philippine Children
Seroprotection Rate and Geometric Mean Titer Up to 24 Months After Booster

+ 148 children received a booster* 12 months after primary series, mean age 5.6 years at booster
+ The booster increased SPR to 100%, this level was sustained for 2 years
+ As in adults, GMT increased about 40-fold after the booster, and remained higher compared with GMT 2 months after primary series

* Booster dose was 0.25 mL for children <3 years and 0.5 mL for children aged 3 years and above, by the time the booster was administered
Dubischar-Kastner et al., Abstract P 2.8, 5th Northern European Conference on Travel Medicine, June 5-8 2014 Bergen, Norway;
Dubischar-Kastner et al., Abstract FC2.04, Presented at the 14th Conference of the International Society of Travel Medicine, May 25-28 2015, Quebec, Canada
**IXIARO Booster in Philippine Children**

**Overview of AE Rates 4 Weeks after Booster**

+ Most AE were mild or moderate
+ Most common AEs: local reactions, fever, loss of appetite, headache, all <10%
+ Two SAEs occurred within 4 weeks after booster:
  › Abscess right flank (0.25 mL dose)
  › Dengue Fever (0.5 mL dose)

<table>
<thead>
<tr>
<th>Subjects with</th>
<th>IXIARO 0.25 mL</th>
<th>IXIARO 0.5 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=81 n (%)</td>
<td>N=67 n (%)</td>
</tr>
<tr>
<td>Any AE*</td>
<td>24 (29.6)</td>
<td>25 (37.3)</td>
</tr>
<tr>
<td>Any solicited local AE</td>
<td>4 (4.9)</td>
<td>8 (11.9)</td>
</tr>
<tr>
<td>Any Serious or Medically Attended AE*</td>
<td>10 (12.3)</td>
<td>3 (4.5)</td>
</tr>
</tbody>
</table>

* Contains solicited and unsolicited AEs
Summary and Conclusions

+ In a small, mainly adolescent pediatric cohort from JEV non-endemic regions, antibody titers declined considerably up to Month 36 after vaccination with IXIARO, but the seroprotection rate was still high at 89.5% (17/19 subjects)

+ In a larger pediatric cohort from a JEV-endemic country, antibody titers also declined considerably up to Month 36; seroprotection rates remained >80% in all age groups. Natural boosting through JEV virus exposure may have contributed to persistence of antibodies in this trial.

+ Together, data suggest a booster may not be absolutely necessary in any pediatric age group for a minimum of 3 years after the primary series

+ However, titers in children declined substantially within the first year after primary series, and long-term seroprotection rate was enhanced by a booster dose, which was well tolerated

+ Valneva considers administration of a booster dose in children 12 months after primary series justified for programmatic reasons (i.e. uniformity of medical use for adults/children and optimization of long-term protection)

Note: Safety / efficacy of a booster or need for a booster in children have not been approved by FDA
Presentation Topics

IXIARO Clinical Data in Adults:
1. Duration of protection following the primary series
2. Duration of protection following a booster dose
3. Regulatory Status: Booster dose recommendations

IXIARO Clinical Data in Children:
1. Duration of protection following the primary series
2. Duration of protection following a booster dose
3. Regulatory Status: Booster dose recommendations
IXIARO Booster Dose Recommendation in Children
Regulatory Status and Outlook

+ In Europe, a first booster recommendation for IXIARO in children is currently under regulatory review
  › There is indication that the adult booster recommendation will be extended for children:
    “A booster dose (third dose) should be given within the second year (i.e. 12 - 24 months) after primary immunization, prior to potential re-exposure to JEV. ...”

+ In the United States, FDA is currently reviewing the pediatric booster data on IXIARO, which were submitted as post-marketing commitment
  › Valneva plans to file a supplemental BLA to FDA in 2016 with proposed edits to the PI for a first booster dose of IXIARO in children
  › The proposed wording for a pediatric booster dose of IXIARO could resemble the adults language in the PI:
    “If the primary series of two doses was completed more than 1 year previously, a booster dose may be given if ongoing exposure or re-exposure to JEV is expected.”

+ No recommendation for a second booster dose of IXIARO in children will be available in either Europe or the U.S.