New Clinical Data for IXIARO® Japanese Encephalitis Vaccine, Inactivated, Adsorbed

February 24, 2016

Katrin Dubischar
Valneva Austria GmbH

valneva

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, <u>both</u> 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)

Study	Follow-Up After Primary Series (Reviewed by ACIP)	Follow-Up After Primary Series (New Data)	Follow-Up After Booster (Reviewed by ACIP)	Follow-Up After Booster (New Data)
IC51-303	36 months	**60 months**	Not Done	
IC51-311	15 months		12 months (all subjects)	**76 months (subgroup)**
IC51-305	24 months		13 months	

Long-Term Immunogenicity Study

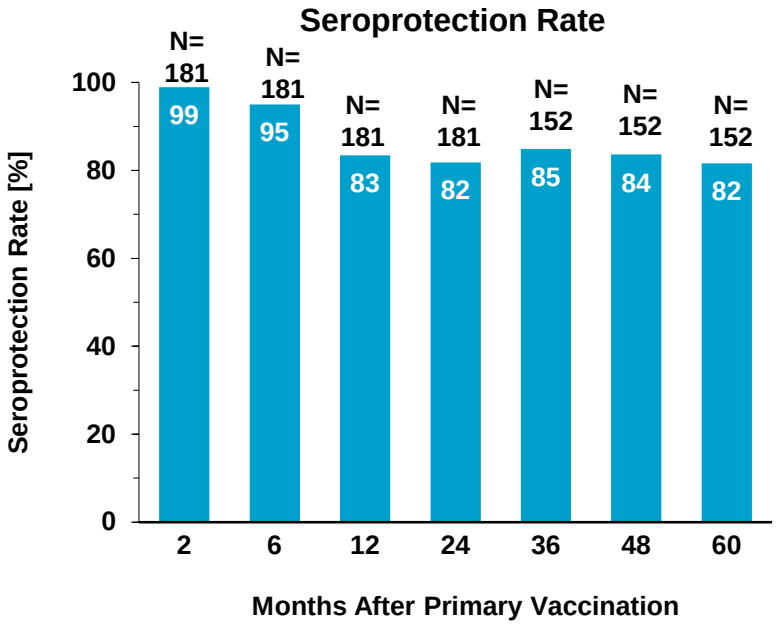
Study Design for Trial IC51-303

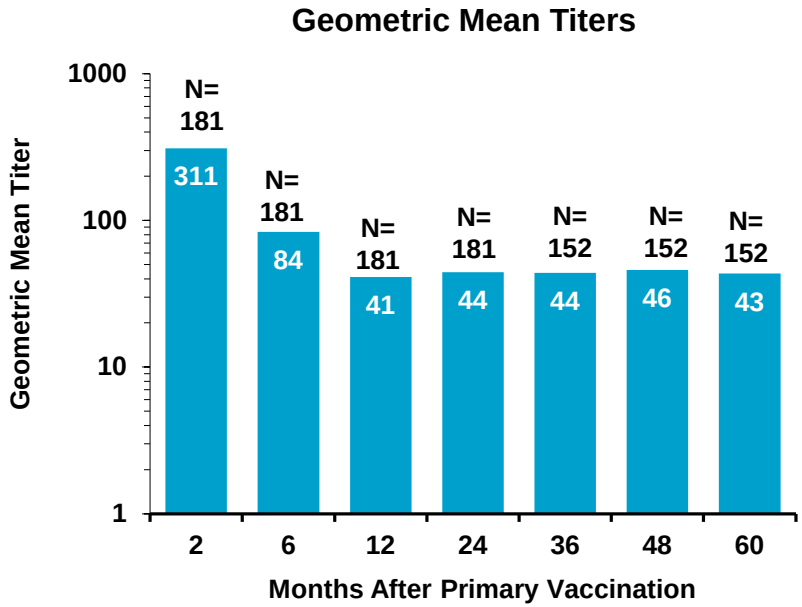
Objectives	Long-term Immunogenicity and Safety
Study Population	181 Subjects ≥18 years of age, vaccinated in previous studies (Days 0 and 28)
Design	Single-arm, Phase 3 Follow-up Study
Treatment Groups	No treatment administered N=181 (up to Month 24) N=152 (up to Month 60)
Follow-up	2, 6,12, 24, 36,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

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



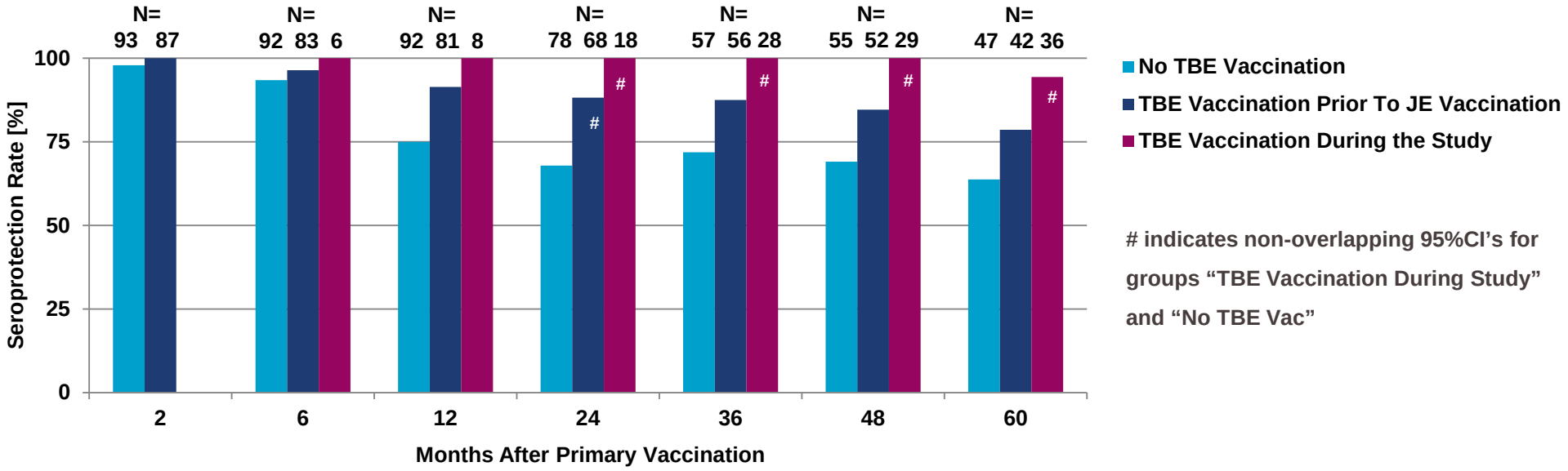


Schuller et al 2008, Dubischar-Kastner et al. Abstract LB-2357, American Society of Tropical Hygiene 2011;

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



1 Dubischar-Kastner et al. Abstract LB-2357; American Society of Tropical Medicine and Hygiene 2011

IXIARO Main Booster Trial

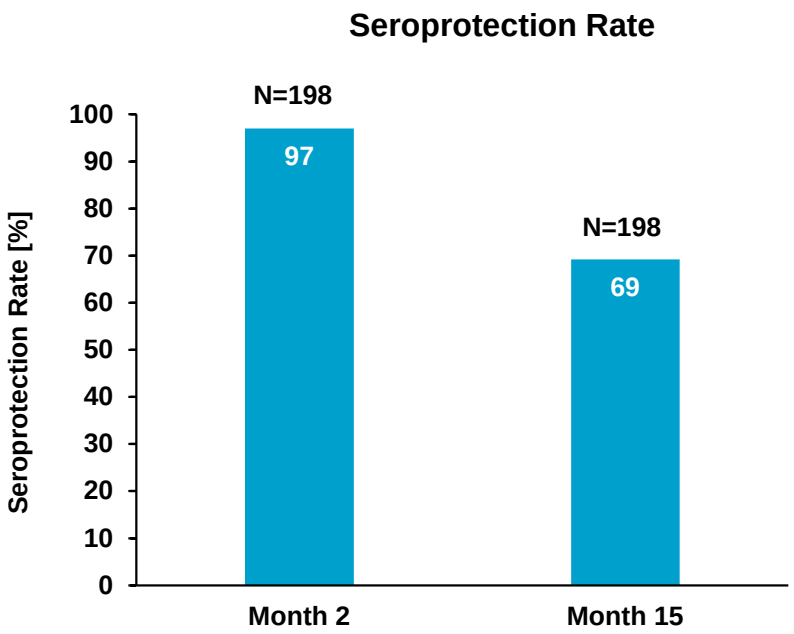
Study Design for Trial IC51-311

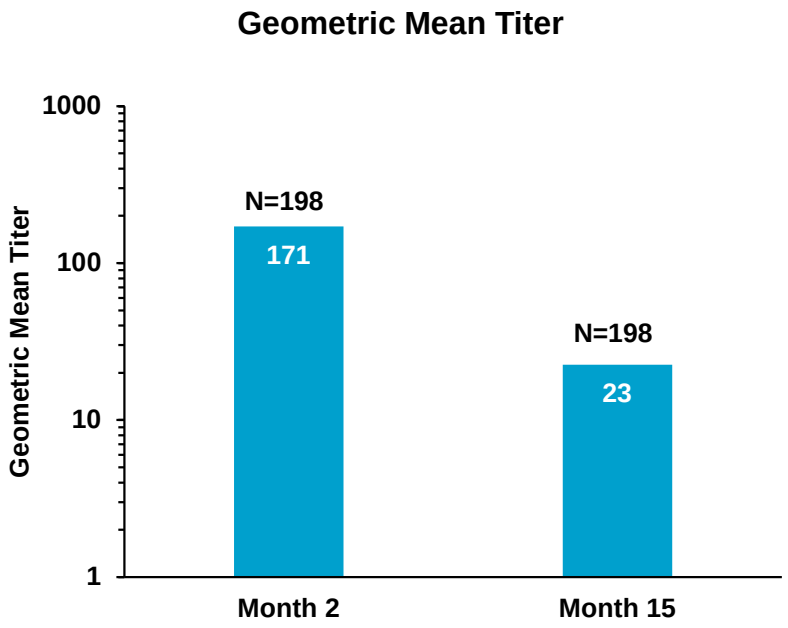
Objectives	Effect of a Booster Dose on Long-term Immunity
Study Population	198 Subjects ≥18 Years of Age
Design	Single-Arm, Open-Label Follow-Up Study
Treatment Group	IXIARO Booster 0.5 ml, i.m. at Month 15 after Primary Immunization, N = 198
Follow-up	1, 6 and 12 Months after the Booster
Countries / Sites	3 Study Sites in Austria and Germany
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

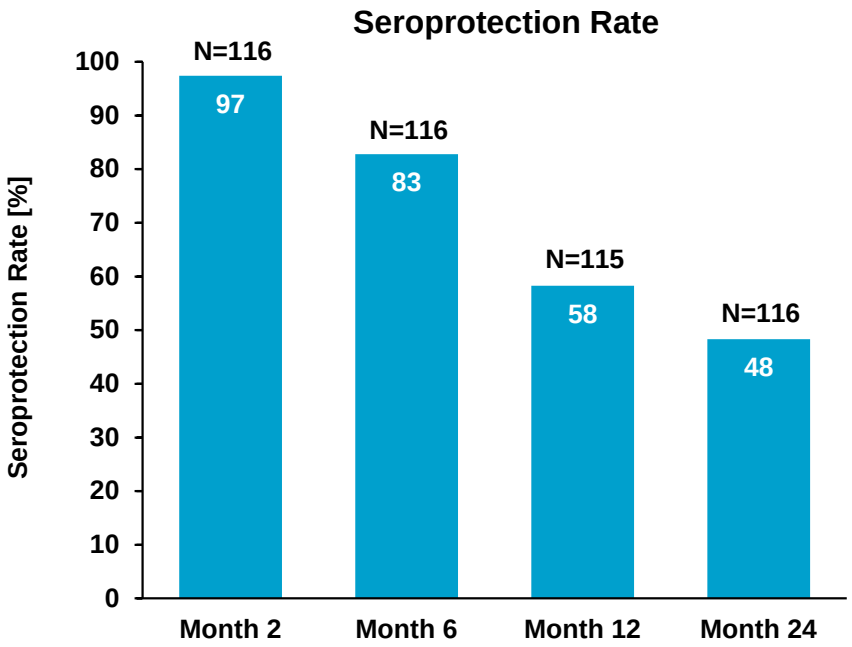
Study Design for Trial IC51-305

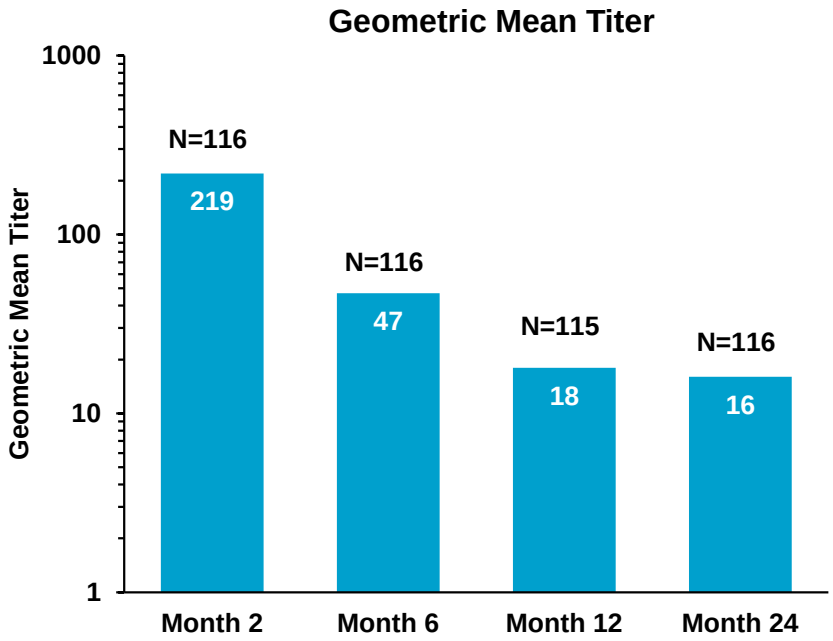
Objectives	Long-term immunogenicity; Response to booster dose in subjects without measurable antibody titers
Study Population	356 subjects ≥18 years of age who received one of three different doses / schedules of IXIARO in a preceding trial Only data for standard schedule group shown here
Design	Open-Label, Phase 3 Follow-up Study
Treatment Group	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
Follow-up	2 years after primary series Up to 12 months after booster
Countries / Sites	2 study sites in Germany and Northern Ireland
Endpoints	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

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





Dubischar-Kastner et al Vaccine 2010

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

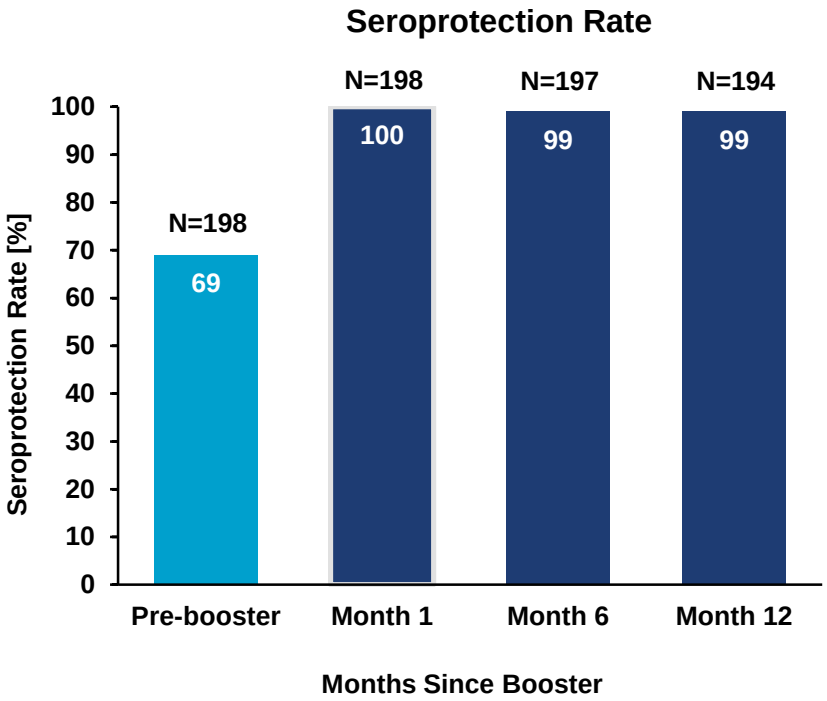
IXIARO Clinical Data in Children:

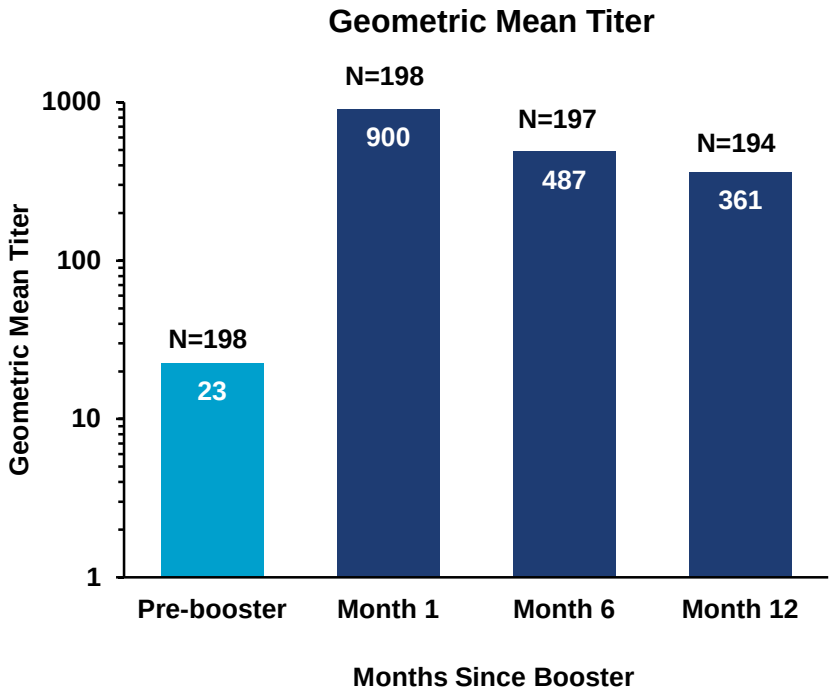
1. Duration of protection following the primary series
2. Duration of protection following a booster dose
3. Regulatory Status: Booster dose recommendations

IXIARO Main Booster Trial

Neutralizing Antibodies at 1, 6 and 12 Months After Booster

+ 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

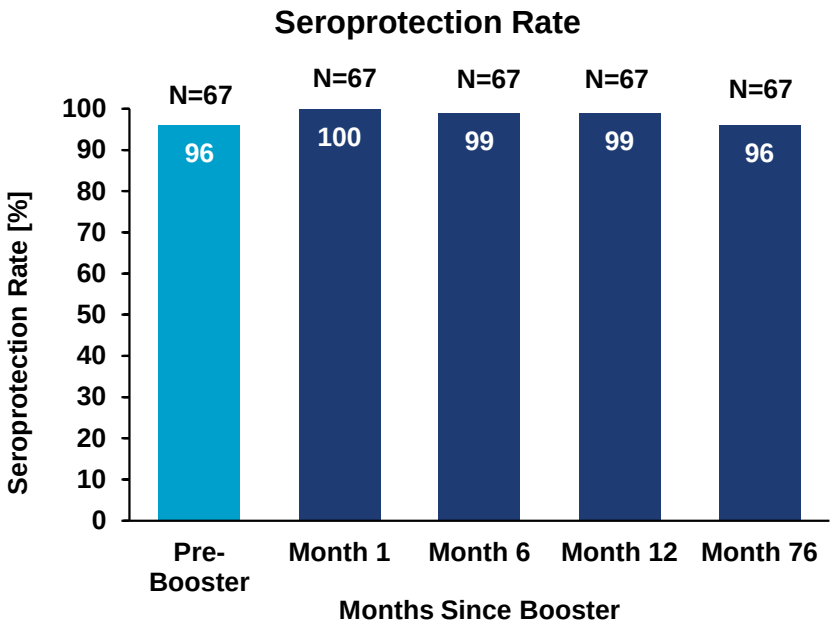


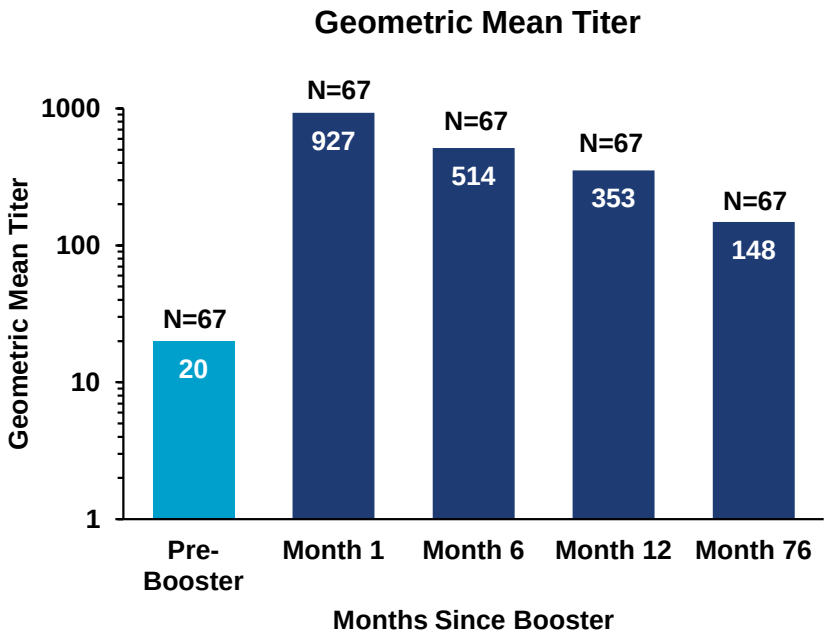


6-Years Extension Trial to IXIARO Main Booster Trial

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

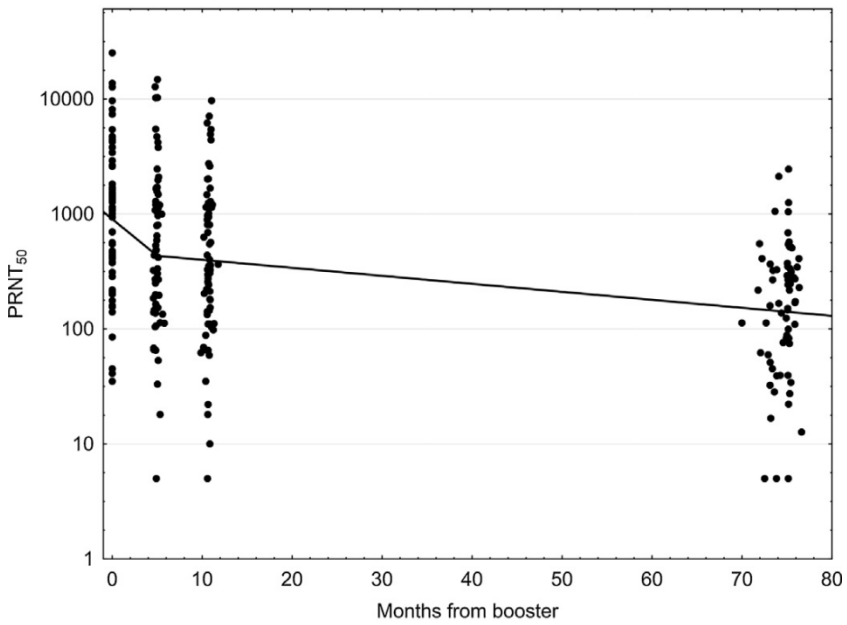
Paulke-Korinek et al, Persistence of Antibodies Six Years after Booster Vaccination with Inactivated Vaccine against Japanese Encephalitis. Vaccine 2015

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

Antibody Decline Kinetics



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

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

* 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

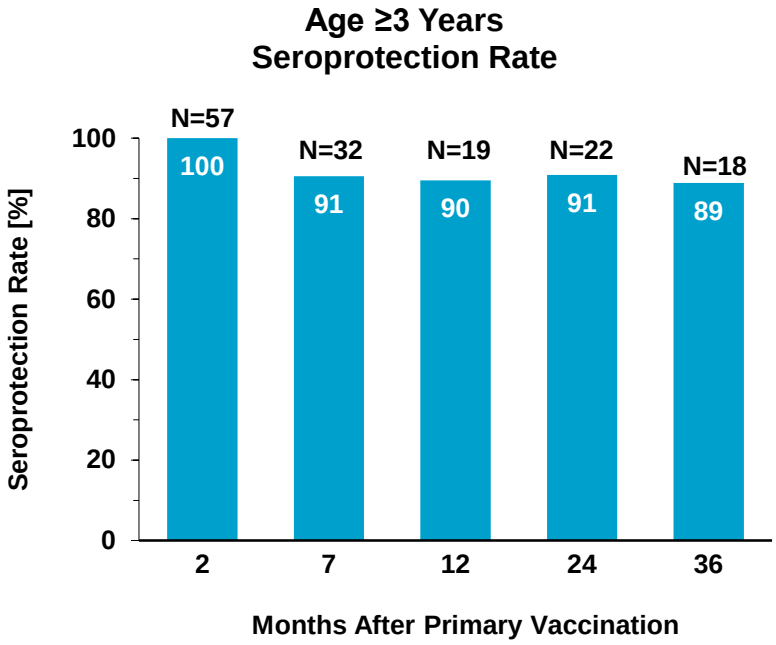
Objectives	Safety and Immunogenicity of IXIARO in a JEV Naïve, Pediatric Travelers Population
Study Population	Children and adolescents, ≥2 months to <18 years
Design	Open-label, single-arm trial with an extension study: 100 children evaluated for safety 64 children evaluated for immunogenicity 23 children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

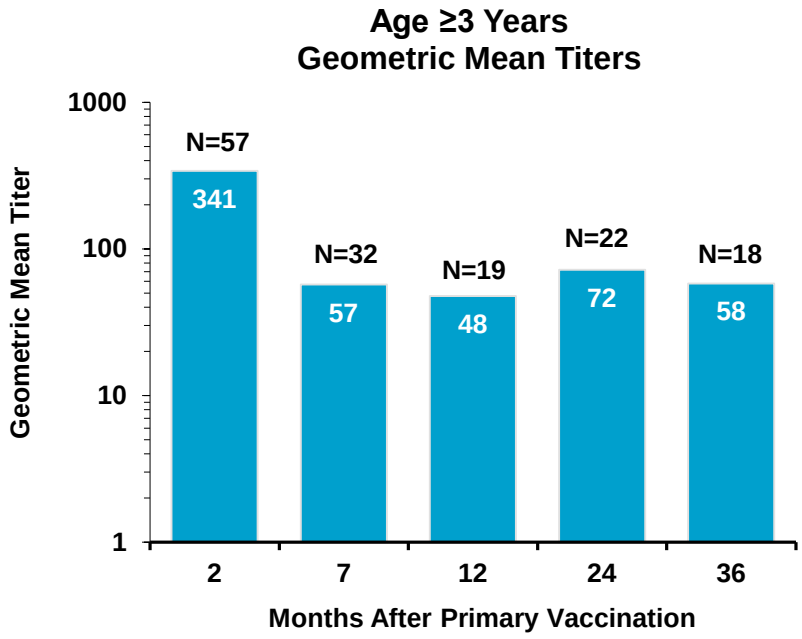
Dubischar-Kastner et al., Abstract P 2.7, 5th Northern European Conference on Travel Medicine, June 5-8 2014 Bergen, Norway
Dubischar-Kastner et al., Abstract FC2.04, Presented at the 14th Conference of the International Society of Travel Medicine, May 25-28 2015, Quebec, Canada

IXIARO Trial in Traveling Children, IC51-322/-324

Seroprotection Rate and Geometric Mean Titer up to Month 36

+ 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





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

IXIARO Antibody Persistence / Booster in Philippine Children[1,2]

Study Design for Trial IC51-325

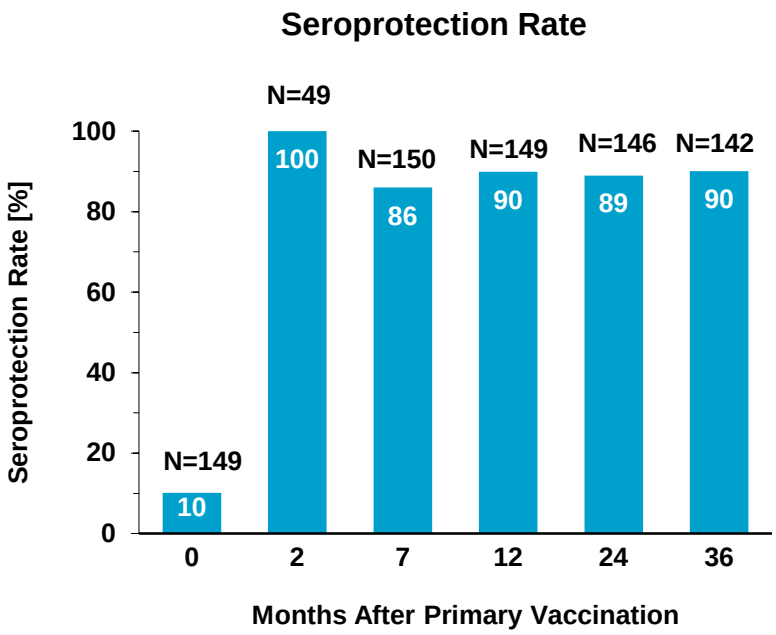
Objectives	Long-term Persistence of Immunity and Safety and Immunogenicity of a IXIARO Booster Dose in Children from JE endemic regions
Study Population	300 children / adolescents aged 2 months – 17 years, vaccinated in preceding trial in endemic region
Design	Open-label, Randomized, Phase 3 Study
Treatment 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

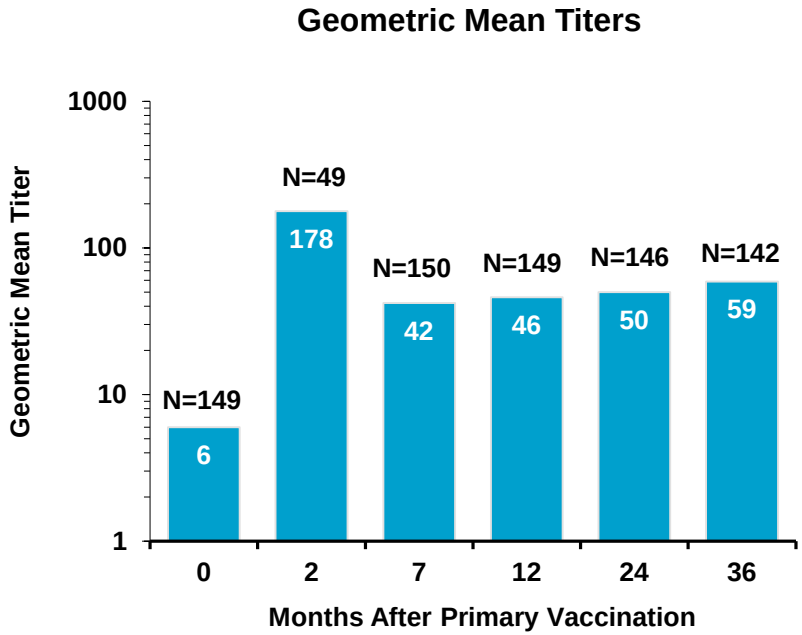
Dubischar-Kastner et al., Abstract P 2.8, 5th Northern European Conference on Travel Medicine, June 5-8 2014 Bergen, Norway
Dubischar-Kastner et al., Abstract FC2.04, Presented at the 14th Conference of the International Society of Travel Medicine, May 25-28 2015, Quebec, Canada

IXIARO 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



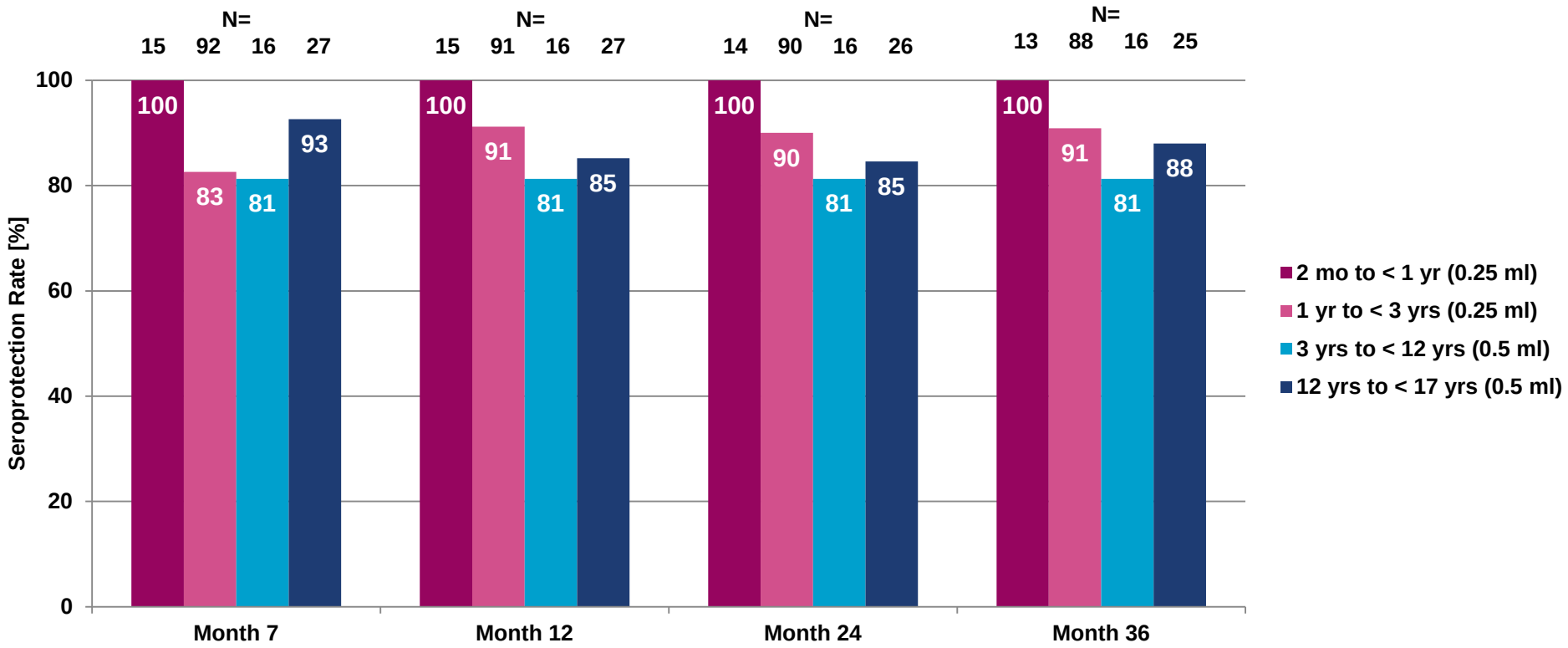


Dubischar-Kastner et al., Abstract P 2.8, 5th Northern European Conference on Travel Medicine, June 5-8 2014 Bergen, Norway
Dubischar-Kastner et al., Abstract FC2.04, Presented at the 14th Conference of the International Society of Travel Medicine, May 25-28 2015, Quebec, Canada

IXIARO Antibody Persistence in Philippine Children

Seroprotection Rate up to Month 36 - Impact of Age

+ Age groups 1 - <3 years and 3 - <12 years showed stronger decline in protection rate down to ~80% at Month 7



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

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

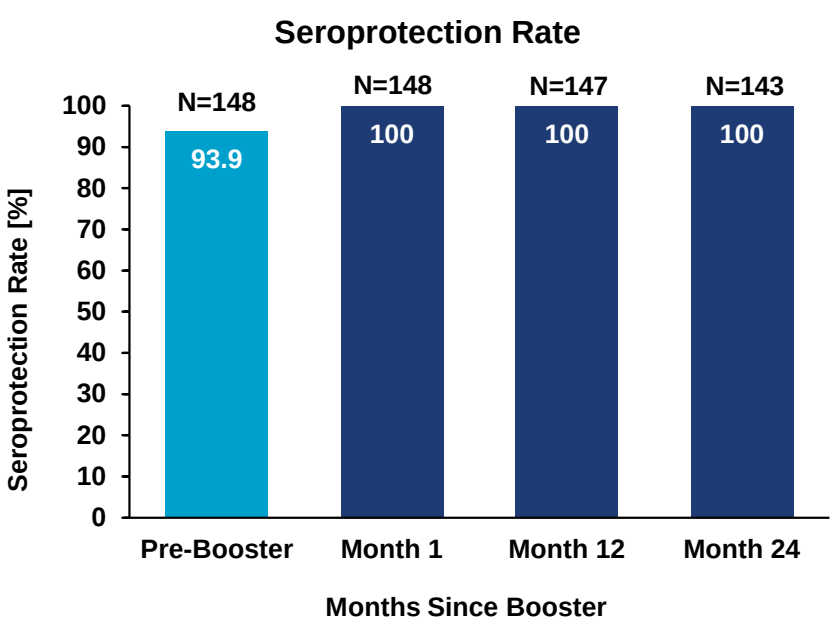
IXIARO Clinical Data in Children:

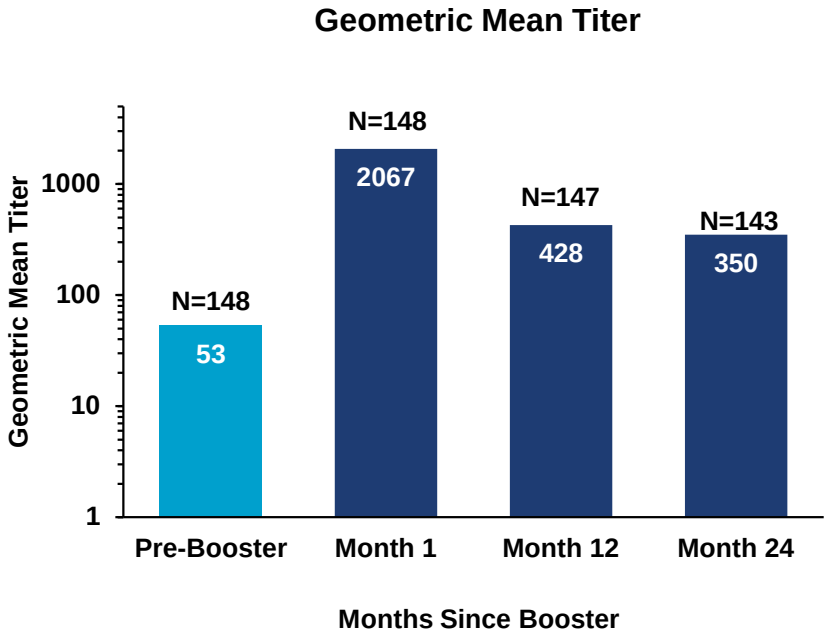
1. Duration of protection following the primary series
2. Duration of protection following a booster dose
3. Regulatory Status: Booster dose recommendations

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)

Subjects with	IXIARO 0.25 mL N=81 n (%)	IXIARO 0.5 mL N=67 n (%)
Any AE*	24 (29.6)	25 (37.3)
Any solicited local AE	4 (4.9)	8 (11.9)
Any Serious or Medically Attended AE*	10 (12.3)	3 (4.5)

* 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.