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

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Presentation Topics

1. **Change in IXIARO® Distributor for the US**
2. Immunogenicity of IXIARO® in Older Adults
3. Accelerated Dosing Schedule for IXIARO® and Concomitant Administration with Rabies Vaccine

Change of U.S. Distributor for IXIARO from GSK to Valneva

+ Novartis Vaccines was the U.S. distributor of IXIARO from FDA approval in 2009 to February 2015
+ In March 2015, GSK acquired U.S. distribution rights to IXIARO as part of a multi-product transaction with Novartis
+ In June 2015, Valneva announced termination of the marketing & distribution Agreement for IXIARO with GSK. Valneva plans to handle these commercial activities on its own and with already established vaccine distributors / wholesalers
+ Transition from GSK to Valneva is anticipated to be completed by year-end 2015
+ Both GSK and Valneva are fully committed to a smooth transition to ensure:
    1. Continuous supply of IXIARO to patients & customers
    2. Ongoing access to medical affairs and pharmacovigilance for IXIARO

Presentation Topics

1. Change in IXIARO® Distributor for the US

2. **Immunogenicity of IXIARO® in Older Adults**

3. Accelerated Dosing Schedule for IXIARO® and Concomitant Administration with Rabies Vaccine

IXIARO in Elderly (≥65 Years of Age)[1]

Study Design for Trial IC51-315

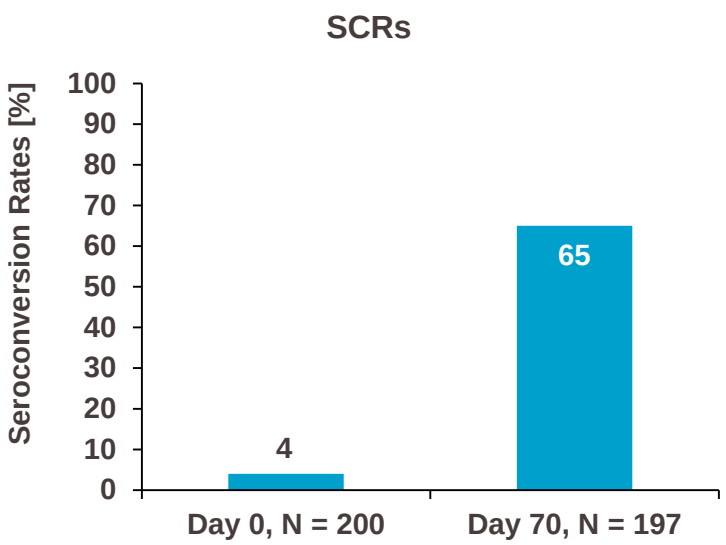
Objectives	Safety and Immunogenicity of IXIARO® in the Elderly
Study Population	Subjects ≥65 Years of Age; including subjects with stable underlying conditions like hypercholesterolemia, hypertension, cardiovascular disease or non insulin-dependent diabetes mellitus
Design	Open-label, Single Arm Study
Treatment Groups	IXIARO, 0.5 ml, i.m. on Days 0 and 28; N = 200
Follow-up	Day 70: Safety and Serology F/U Month 7: Safety F/U Phone Call
Countries / Sites	5 Study Sites in Germany and Austria
Endpoints	Primary EP*: Rate of SAEs§ and medically attended AEs§ until Day 70 Main Secondary EPs: • Rate of subjects with SAEs and medically attended AEs until Month 7 • Unsolicited Adverse Events until Day 70 and Month 7 • Solicited Adverse Events 7 days after each dose • Immunogenicity (SCRs+/GMTs#) at Day 70

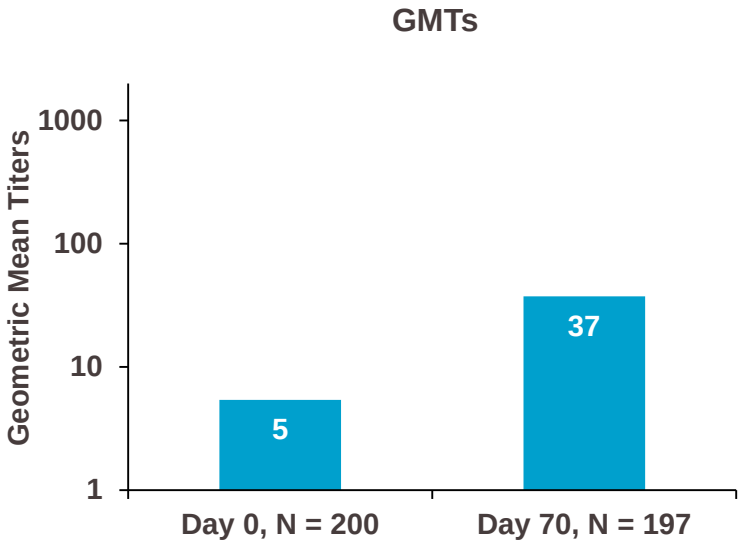
1 Dubischar-Kastner et al, Abstract PO14.04 Presented at the 13th Conference of the International Society of Travel Medicine, Maastricht, NL, May 2013
* EP = Endpoint + Seroconversion Rate (SCR) defined as Rate of Subjects with Neutralizing Antibody Titer of ≥1:10 in a 50% Plaque Reduction Neutralization Test ($PRNT_{50}$)
# GMT = Geometric Mean Titer for Neutralizing Antibodies determined by 50% Plaque Reduction Neutralization Test ($PRNT_{50}$)
§ (S)AE = (Serious) Adverse Event

Immunogenicity of IXIARO in Elderly (≥65 Years of Age)[1]

Geometric Mean Titers[#] and Seroconversion Rates[+] at Day 70

+ **Immune response to IXIARO in elderly is lower compared to younger adults**
  - › SCR of 96% and GMT of 240 were seen in younger adults in the pivotal licensure trial[2]





[+] Seroconversion Rate (SCR) defined as Rate of Subjects with Neutralizing Antibody Titer of ≥1:10 in a 50% Plaque Reduction Neutralization Test ($PRNT_{50}$)
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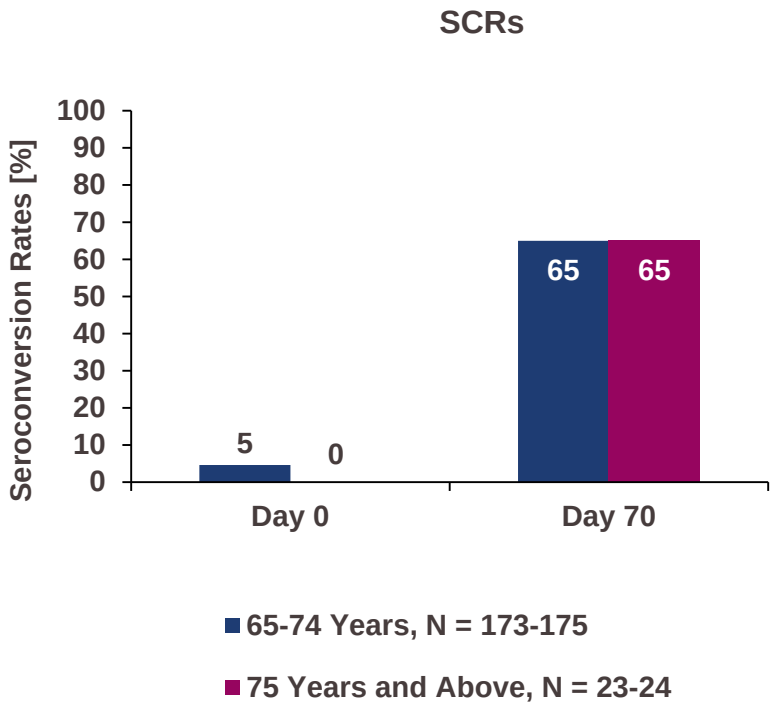
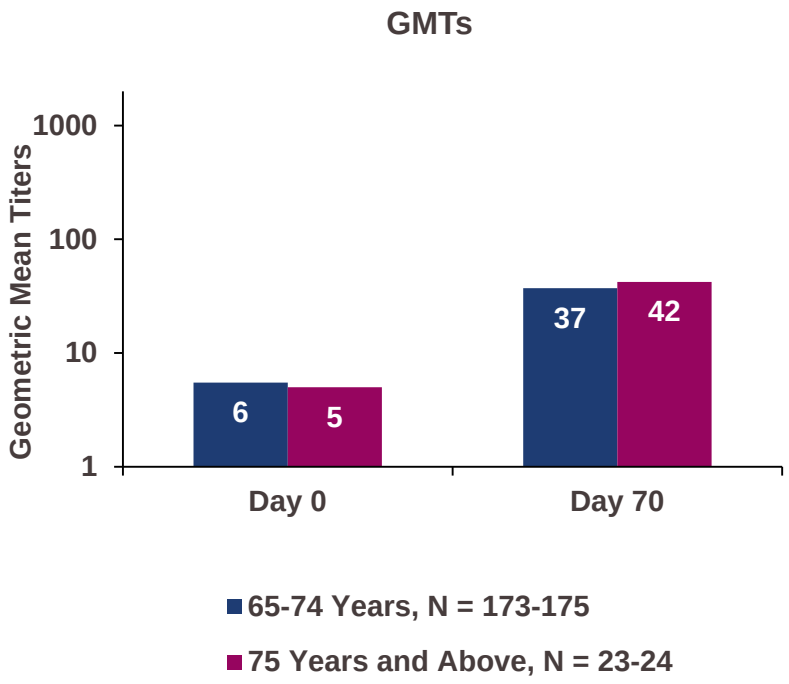
1 Dubischar-Kastner et al, Abstract PO14.04 Presented at the 13th Conference of the International Society of Travel Medicine, Maastricht, NL, May 2013
2 IXIARO Prescribing Information

Immunogenicity of IXIARO in Elderly (≥65 Years of Age)[1]

GMTs[#] and SCRs[+] Stratified by Age Group

+ Immune responses in age groups 65 to 74 years and ≥75 years are similar





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IXIARO in Elderly

Conclusions and Considerations on Booster Dose Timing

+ Similar to other vaccines, IXIARO shows lower seroconversion rates and GMTs in elderly compared to younger adults

+ Advanced age ≥75 years (range 75-83) has no further impact on GMTs and SCRs

+ No long-term data were gathered in this population. Duration of protection is thus uncertain, especially as immune response to the primary series is low

+ Elderly may benefit from a booster before further exposure to JEV

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3. **Accelerated Dosing Schedule for IXIARO® and Concomitant Administration with Rabies Vaccine**

Use of Japanese Encephalitis Vaccine among U.S. Travelers[1]

+ Study in Global TravEpiNet sites (CDC-sponsored Consortium of U.S. clinical practices providing pre-travel care) from September 2009 to August 2012 (i.e., after introduction of IXIARO®)
+ Only 50% of travelers at higher risk for JE presented in time for the FDA-approved, two-dose (days 0 & 28) schedule of IXIARO

Travelers	Higher Risk Travelers (n = 711)	Lower Risk Travelers (n = 7,578)
Days to Departure at Clinic Visit (%)		
0–13	25.7	30.5
14–20	12.5	14.1
21–27	11.7	12.1
>28	**50.1**	**43.3**
JE Vaccination Status (%)		
Vaccinated within previous 2 years	1.5	0.4
Received vaccine for this itinerary	26.8	4.0
Not vaccinated	71.6	95.7

[1] Deshpande et al., Use of Japanese Encephalitis Vaccine in US Travel Medicine Practices in Global TravEpiNet. AmJTropMedHyg 2014

IXIARO Accelerated Dosing and Concomitant Use with Rabies Vaccine Study[1,2]

Observer-blinded, Randomized, Phase III Study in Adults 18-65 Years

Group	No of Subjects Enrolled	Schedules	Day 0	Day 3	Day 7	Day 28	Follow-up
			Vaccines Administered				
1	167	Conventional JE vaccine + Rabies	**IXIARO** Rabipur	Placebo	Placebo Rabipur	**IXIARO** Rabipur	7 and 28 days post-dose 2 6 and 12 months after start of series
2	217	Accelerated JE vaccine + Rabies	**IXIARO** Rabipur	Rabipur	**IXIARO** Rabipur	Placebo Placebo	
3	221	Conventional Rabies vaccine alone	Rabipur Placebo	Placebo	Rabipur Placebo	Rabipur Placebo	
4	56	Conventional JE vaccine alone	**IXIARO** Placebo	Placebo	Placebo Placebo	**IXIARO** Placebo	

Study was sponsored and conducted by Novartis Vaccines and Diagnostics
JEV serological testing was performed by Valneva
Rabipur® is identical to US-licensed Rabavert®

1 Jelinek T et al. J Travel Med, 22: 225–231. doi:10.1111/jtm.122102
2 Cramer et al. Abstract LB-3134, presented at 63rd Annual Meeting ASTMH, New Orleans, USA, November 2014

IXIARO Accelerated Dosing and Concomitant Use with Rabies Vaccine Study

Study Endpoints with Relevance for JE Vaccine

+ **Primary endpoint: JE accelerated schedule**

  › **Non-inferiority of SCR 28 days after the last active immunization**, Groups “Accelerated JE vaccine with Rabies” versus “Conventional JE vaccine alone”

  - Margin set to 10%
  - Accelerated schedule was considered non-inferior to the conventional schedule if the lower bound of the two-sided 97.5% CI of the difference in the percentages of subjects with $PRNT_{50}$ titer ≥1:10 measured 28 days after last active vaccine administration was greater than -10%

+ **Secondary endpoint: JE + Rabies vaccines concomitant administration**

  › **Non-inferiority of $PRNT_{50}$ GMT measured 28 days after last active immunization**, Groups “Conventional JE vaccine with Rabies” versus “Conventional JE vaccine alone”

  - Margin set to GMT ratio of 0.5 (Concomitant administration / JE vaccine alone)

IXIARO Accelerated Dosing Schedule

Study Population Demographic Data

	R/JE-Conv N=167 n (%)	R/JE-Acc N=217 n (%)	JE-Conv N=56 n (%)
Mean Age, years (SD)	37.3 (13.4)	36.8 (12.7)	38.8 (13.3)
Female	46%	59%	54%
Male	54%	41%	46%
Mean Weight (kg)	76	75	75
Mean Height (cm)	175	172	173

IXIARO Accelerated Dosing Schedule:

Primary Endpoint: Non-inferiority for Seroconversion Rate* 28 Days After Last Active Dose

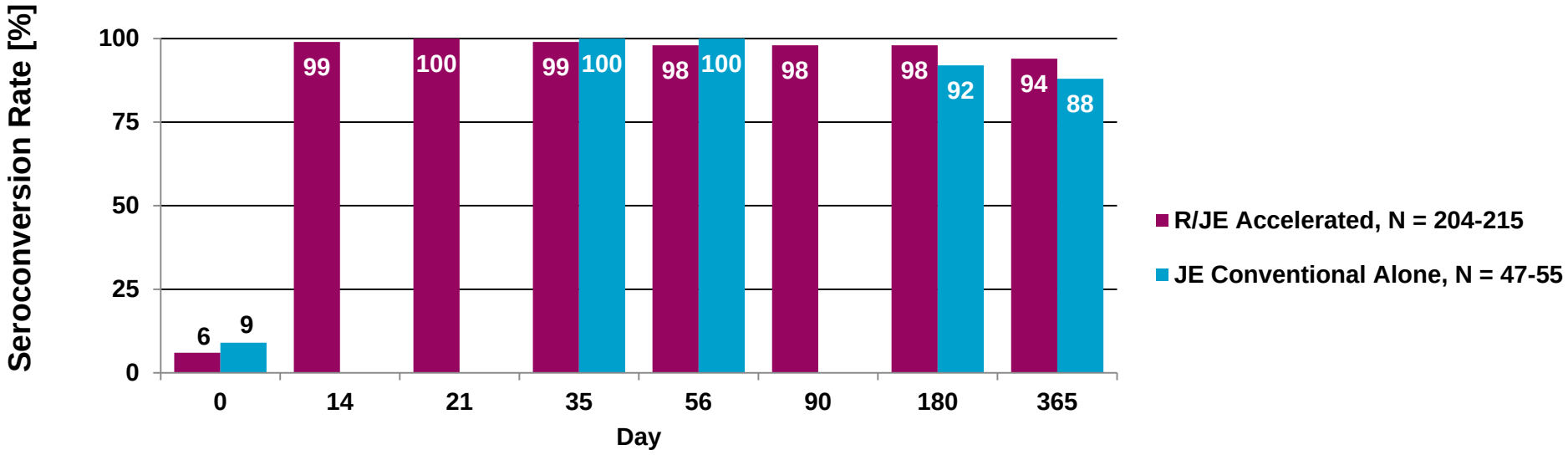
+ **Non-inferiority of the accelerated schedule for SCR established:**
  - › Lower bound of the 95% Confidence Interval for the SCR difference between groups R/JE-Accelerated - JE-Conventional was above -10%

	R/JE-Acc % (n/N)	JE-Conv % (n/N)	R/JE-Acc - JE-Conv
Day 0	**6%** (13/215)	**9%** (5/55)	
28 days after last active dose	**99%** (203/206)	**100%** (49/49)	**-1% (-4.8%, 7.9%)**

*SCR defined as JEV Neutralizing Antibody Titer of $PRNT_{50}$≥1:10

IXIARO Accelerated Dosing Schedule:
Kinetics of Seroconversion for JEV Neutralizing Antibodies

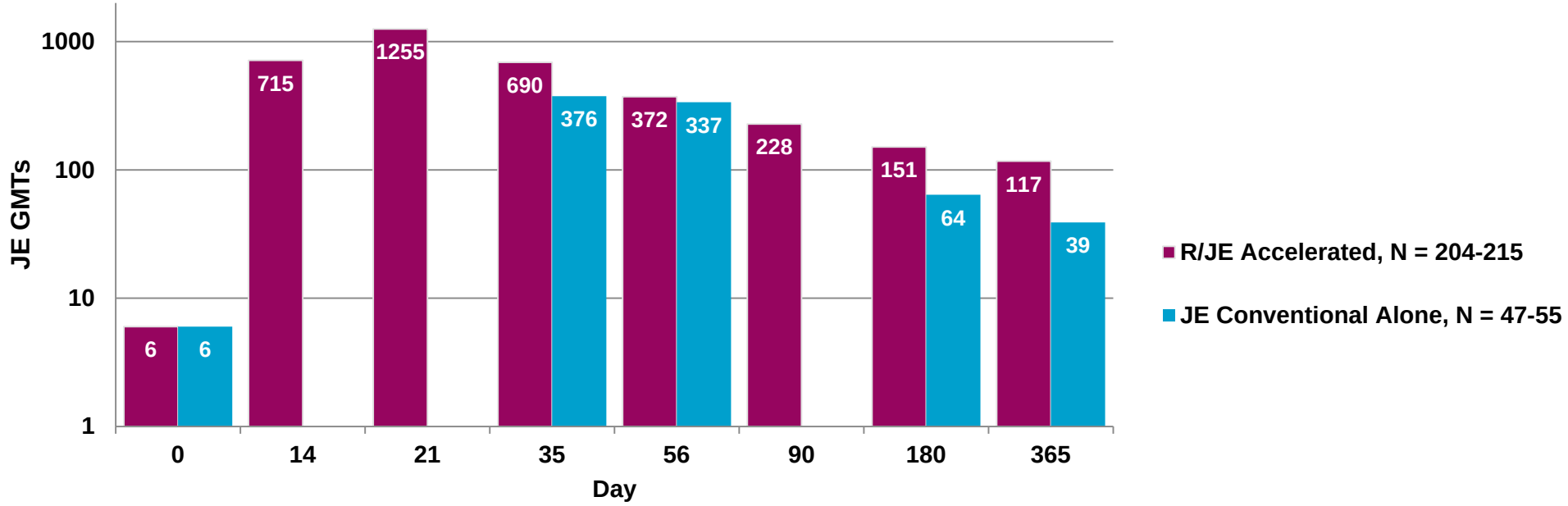
+ **Rapid onset of immune response with accelerated schedule**
  - › SCR* 99% at Day 15 (7 days after last active JE vaccination)
  - › SCR* remains high for 12 months after vaccination



*SCR defined as JEV Neutralizing Antibody Titer of $PRNT_{50}$≥1:10

IXIARO Accelerated Dosing Schedule:
Kinetics of GMTs for JEV Neutralizing Antibodies

+ **Accelerated schedule resulted in higher GMTs**
  - › About 3-fold higher maximum GMT compared to conventional schedule
  - › GMT after accelerated schedule remained higher at Day 365



*SCR defined as JEV Neutralizing Antibody Titer of $PRNT_{50}$≥1:10

IXIARO Concomitant Administration with Rabies Vaccine:
Secondary Endpoint: Non-inferiority for GMT* 28 Days After Last Active Dose

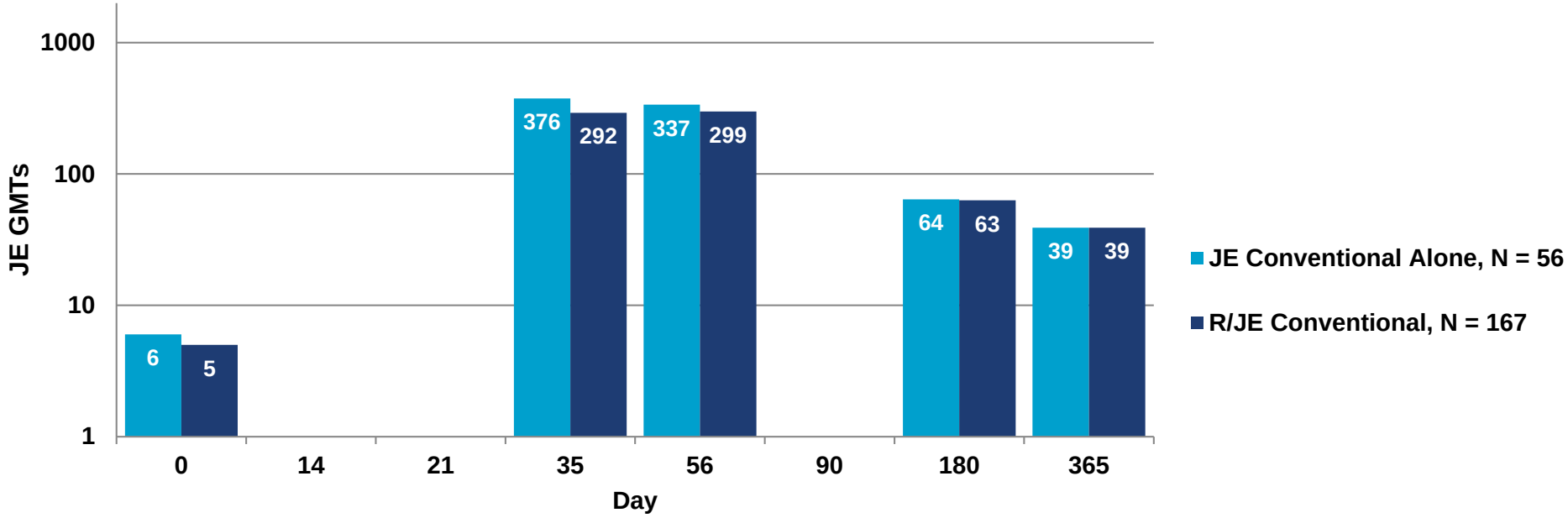
+ **Non-inferiority of the concomitant administration with Rabies vaccine established:**
  - › Lower bound of the 95% Confidence Interval of the ratio of GMTs of R/JE-Conv versus JE-Conv was greater than 0.5

	R/JE-Conv GMT [95%CI]	JE-Conv GMT (N) [95%CI]	Ratio R/JE-Acc / JE-Conv
Day 0	**5.1** [4.9; 5.3]	**5.7** [5.3; 6.1]	
28 days after last active dose	**291** [256; 331]	**331** [265; 415]	**0.88 [0.68; 1.13]**

*GMT determined by Plaque Reduction Neutralizing Test

IXIARO Concomitant Administration with Rabies Vaccine:
Kinetics of GMTs for JEV Neutralizing Antibodies

+ **Concomitant administration with Rabies vaccine did not impact GMT**
  - › GMTs were comparable after combined administration versus administration of IXIARO alone



*GMT determined by Plaque Reduction Neutralizing Test

IXIARO Accelerated Dosing Schedule and Concomitant Administration with Rabies Vaccine:

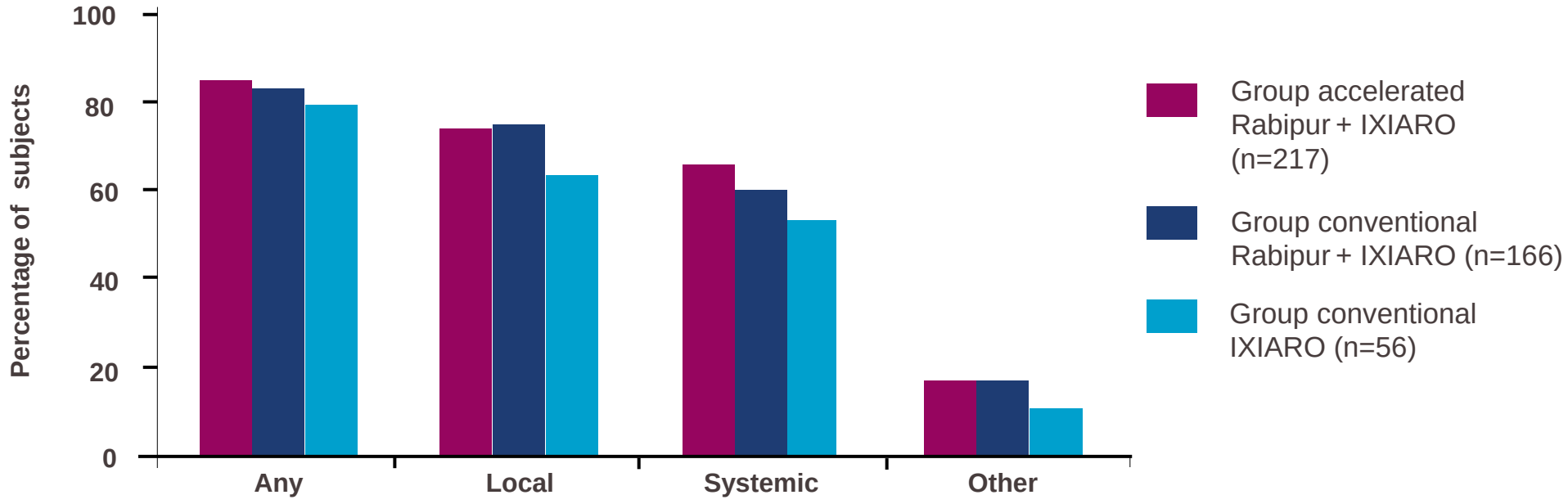
Overview of Adverse Events

	R/JE-Conv N=166 n (%)	R/JE-Acc N=217 n (%)	JE-Conv N=56 n (%)
Any AE (Solicited and Unsolicited)	140 (84)	191 (88)	49 (88)
Solicited AEs	137 (83)	185 (85)	44 (79)
Unsolicited AEs	69 (42)	108 (50)	29 (52)
Severe Related Unsolicited AEs	2 (1)	4 (2)	1 (2)
Related SAEs	0 (0)	0 (0)	1 (2)

IXIARO Accelerated Dosing Schedule and Concomitant Administration with Rabies Vaccine:

Solicited Adverse Reactions 7 Days After Any Dose

+ **Vaccine safety profile was generally similar across the groups**
  - › Local solicited reactions were reported by 63%–75% of subjects across groups
  - › Systemic solicited reactions were observed in 54%–66%



IXIARO Accelerated Dosing Schedule / Concomitant Administration with Rabies Vaccine:

Conclusions

+ The licensed immunization schedule for IXIARO consists of two doses, 4 weeks apart
  - › A high number of international travelers present too short of departure to complete this primary immunization schedule[1]

+ JE vaccine, administered according to an accelerated dosing schedule (one week interval between the 2 doses), induced short-term immune responses which were non-inferior to those obtained following the licensed immunization schedule[2]
  - › This accelerated dosing schedule is not approved in the U.S.

+ The accelerated dosing schedule resulted in titers that were consistently higher than with the conventional schedule both mid-term (6 months) and long-term (1 year)[3]

+ Both immunogenicity and safety results supported concomitant administration of JE and rabies vaccines, according to both the accelerated and conventional schedules

1 Deshpande et al., Use of Japanese Encephalitis Vaccine in US Travel Medicine Practices in Global TravEpiNet. AmJTropMedHyg 2014
2 Jelinek T et al. J Travel Med, 22: 225–231. doi:10.1111/jtm.12210
3 Cramer et al. Abstract LB-3134, presented at 63rd Annual Meeting ASTMH, New Orleans, USA, November 2014

Regulatory Review and Updates to IXIARO Labelling

Use in Elderly & Accelerated Dosing Schedule

+ Use in Elderly update to European labelling was approved April 2015[1]

  "As with many vaccines, the immune response in older persons (≥65 years of age) to IXIARO is lower than in younger adults. Duration of protection is uncertain in older persons, therefore a booster dose (third dose) should be considered before any further exposure to JE virus."

+ Accelerated Dosing Schedule was approved in Europe April 2015[1]

  "Persons aged 18-65 years can be vaccinated in a rapid schedule as follows: First dose at Day 0. Second dose: 7 days after first dose."

  - The European recommendation to administer a booster dose of IXIARO after 12 months if risk for JE exposure persists, remains unchanged

+ Valneva is exploring possible approaches to update the IXIARO Prescribing Information with these and other new clinical data, and continues to work with FDA on respective plans. Any FDA approved updates to the Prescribing Information for IXIARO would, however, be unlikely to occur before 2017

[1] IXIARO Summary of Product Characteristics, 2015