Pediatric Data for IXIARO® Japanese Encephalitis Vaccine, Inactivated, Adsorbed

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IXIARO Clinical Trials for Pediatric Licensure

Study	Design	Number of Subjects
IC51-221: Dose-Confirmation in Toddlers Aged 1 to <3 Years; India[1]	Randomized, Controlled, Open-Label Trial, comparing IXIARO to Korean Green Cross JE vaccine	60
IC51-322: IXIARO in Traveling Children Aged 2 Months to <18 Years; EU, US and Australia[2]	Single-Arm, Open-Label Trial	60
IC51-323: Pivotal Pediatric Trial in Children Aged 2 Months to <18 Years; The Philippines (JEV Endemic Region)[3]	Randomized, Controlled, Open-Label Trial, comparing IXIARO to Havrix®720 and Prevnar7®	1,867

1. Kaltenboeck et al. Immunogenicity and safety of IXIARO (IC51) in a Phase II study in healthy Indian children between 1 and 3 years of age. Vaccine 2010;28:834-9
2. Dubischar-Kastner et al. Interim Safety and Immunogenicity Data for the Inactivated Japanese Encephalitis Vaccine IXIARO®, IC51, in Children from JE non-endemic countries. Presented at the 4th Northern European Conference on Travel Medicine, June 2012, Abstract P.9. Abstract available at http://nectm.com/wp-content/uploads/BookofAbstracts.pdf
3. Dubischar-Kastner et al. Safety and Immunogenicity of the Inactivated Japanese Encephalitis Vaccine IXIARO®, IC51, in Filipino Children aged 2 months to <18 years. Presented at the 4th Northern European Conference on Travel Medicine, June 2012, Abstract P.9. Abstract available at http://nectm.com/wp-content/uploads/BookofAbstracts.pdf

Dose-Confirmation in Toddlers

Study Design for Trial IC51-221

Objectives	Dose-confirmation in Age Group ≥1 to <3 Years
Study Population	60 Healthy Toddlers
Design	Randomized Controlled Trial, Open-Label
Treatment Groups	IXIARO 0.25 mL, i.m. on Days 0 and 28; N = 24 IXIARO 0.5 mL, i.m. on Days 0 and 28; N = 24 0.5 mL JenceVac™ (Mouse-brain derived JE vaccine (virus strain Nakayama) produced by Korean Green Cross), s.c., on Days 0, 7 and 28; N = 12
Follow-up	28 Days After Last Dose (Day 56)
Countries / Sites	1 Center in India (Bangalore)
Endpoints	Primary Endpoint: Seroprotection Rate at Day 56 Geometric Mean Titer for JEV Neutralizing Antibodies at Day 56 Unsolicited Adverse Events Until Day 56 Solicited Adverse Events 7 Days After Each Dose

Dose-Confirmation in Toddlers

Immunogenicity of IXIARO 0.25 mL / 0.5 mL and Comparator JE Vaccine

Seroprotection Rate at Screening, Day 28 and Day 56, Per Protocol Population

» SPR at Day 56 showed **no significant differences between groups**

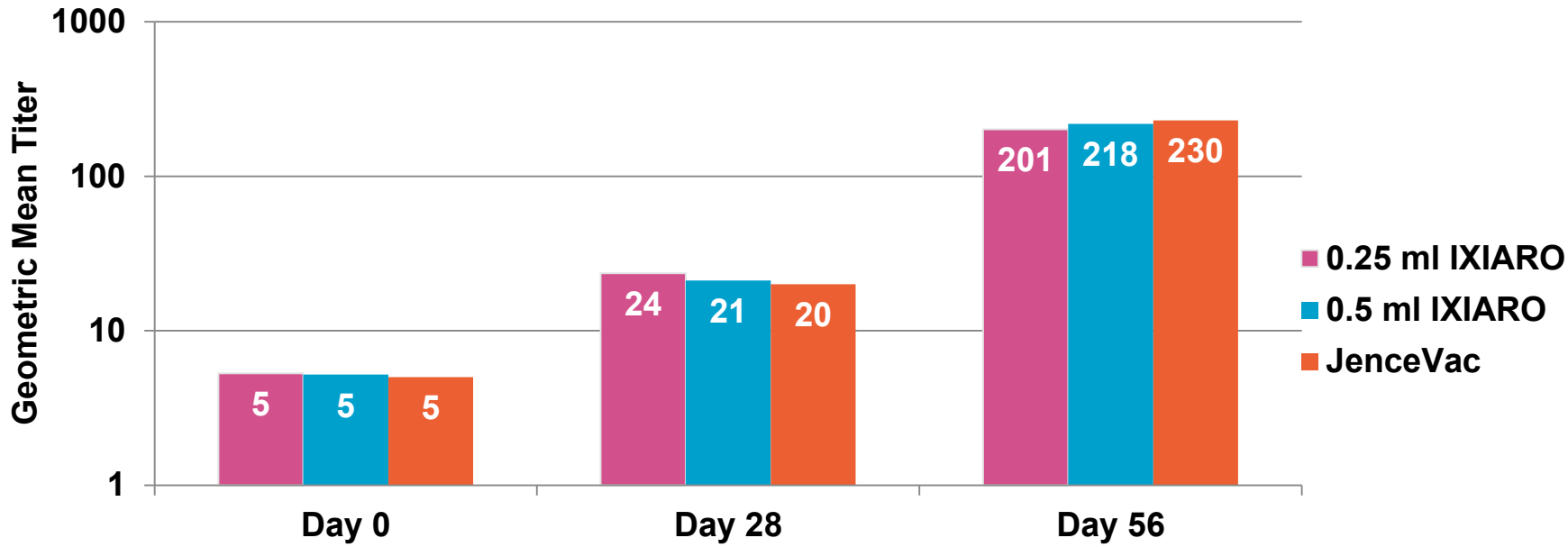
	IXIARO 0.25 mL % (n/N)	IXIARO 0.5 mL % (n/N)	JenceVac % (n/N)
Day 0	4.3 (1/23)	4.8 (1/21)	0
Day 28	65.2 (15/23)	71.4 (15/21)	63.6 (7/11)
Day 56	95.7 (22/23)	95.2% (20/21)	90.9% (10/11)

Dose-Confirmation in Toddlers

Immunogenicity of IXIARO 0.25 mL / 0.5 mL and Comparator JE Vaccine

Geometric Mean Titer at Screening, Day 28 and Day 56, Per Protocol Population

› GMT at Day 56 showed **no significant differences between groups**



Dose-Confirmation in Toddlers:
Adverse Events after IXIARO 0.25 mL / 0.5 mL and Comparator JE Vaccine

Adverse Events up to Day 56, Including Solicited AE for 7 Days After Vaccination

- **No significant differences in AE rates between groups**
- No Serious Adverse Events were reported
- All Adverse Events were mild in nature

	IXIARO 0.25 mL N=24 n (%)	IXIARO 0.5 mL N=24 n (%)	JenceVac N=12 n (%)
Subjects with at least one AE	3 (12.5)	5 (20.8)	4 (33.3)
Fever	0 (0.0)	1 (4.2)	1 (8.3)
Injection Site Tenderness	2 (8.2)	3 (12.5)	3 (25.0)
Skin Lesion	1 (4.2)	0 (0.0)	0 (0.0)
Skin Rash	0 (0.0)	1 (4.2)	0 (0.0)

IXIARO Phase III Pediatric Trial in Traveling Children

Study Design for Trial IC51-322

Objectives	Safety and Immunogenicity of IXIARO in a JEV Naïve, Pediatric Traveler's Population
Study Population	60 Children / Adolescents, Age Group ≥2 Months to <18 Years
Design	Open-label, Single-arm Trial – Interim Analysis
Treatment Groups	IXIARO 0.25 mL, i.m. on Days 0 and 28; <3 Years of Age, N = 5 IXIARO 0.5 mL, i.m. on Days 0 and 28; 3 to <18 Years of Age, N = 55
Follow-up	Day 56 and Month 7 for Immunogenicity and Safety
Countries / Sites	15 Study Sites in Australia, Germany, USA, Denmark, Sweden
Endpoints	Primary Endpoint: Rate of SAE / Medically-attended AEs until Day 56 Immunogenicity (SPR/GMT) at Day 56 and Month 7 Unsolicited Adverse Events until Day 56 and Month 7 Solicited Adverse Events 7 Days After Each Dose

IXIARO in Traveling Children:
Seroprotection Rates after IXIARO 0.25 and 0.5 mL

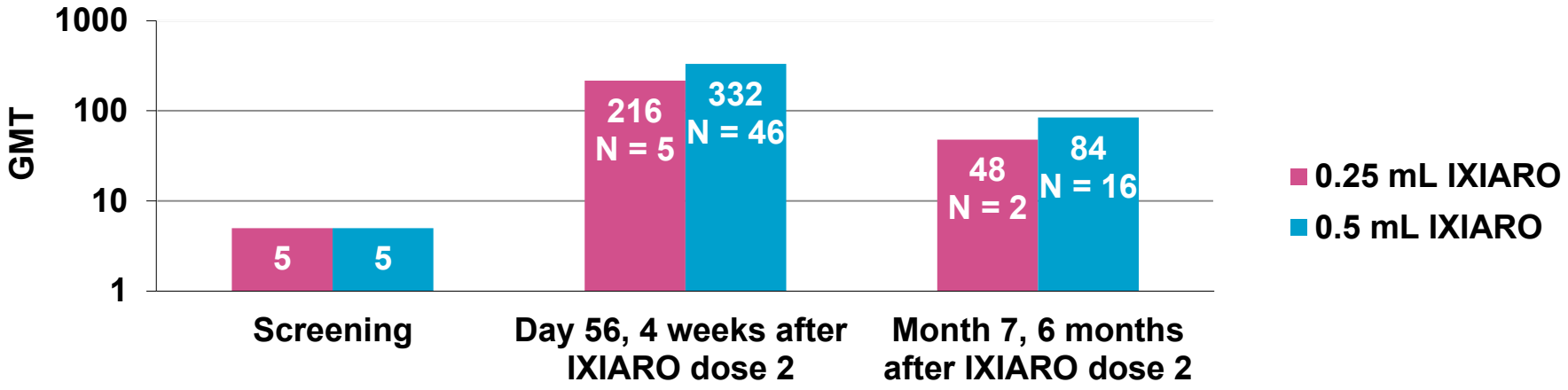
Seroprotection Rate at Screening, Day 56 and Month 7 (Intent-to-Treat Population)

› **Both dose levels led to protective titers in 100% of subjects by 4 weeks after the second dose**

	IXIARO 0.25 mL % (n/N)	IXIARO 0.5 mL % (n/N)
Screening	0 (0/5)	0 (0/49)
Day 56	100 (5/5)	100 (46/46)
Month 7	100 (2/2)	100 (16/16)

IXIARO in Traveling Children:
Neutralizing Antibody Titers after IXIARO 0.25 and 0.5 mL

Geometric Mean Titer, at Screening, Day 56 and Month 7, Intent-to-Treat Population



Geometric Mean Titer for Neutralizing Antibodies determined by 50% Plaque Reduction Neutralization Test ($PRNT_{50}$)

IXIARO in Traveling Children:
Overview of AE Rates to Day 56 after IXIARO 0.25 and 0.5 mL

Safety Analysis Based on 60 Subjects with at Least One Dose of Vaccine

- Overall, 53 subjects followed for at least 4 weeks after dose 2
- Mean age: 12.5 years (10 months - 17 years)

Rate of Subjects with	IXIARO 0.25 mL N=5 n (%)	IXIARO 0.5 mL N=55 n (%)	Total N=60 n (%)
Primary Endpoint: Any SAE/Medically Attended AE	1 (20.0)	2 (3.6)	3 (5.0)
Any Solicited or Unsolicited AE	3 (60.0)	37 (67.3)	40 (66.7)
Any Medically Attended AEs	1 (20.0)	2 (3.6)	3 (5.0)
Any Serious AEs (SAEs)	0	0	0

IXIARO in Traveling Children:
Solicited Adverse Reactions within 7 Days after 0.25 mL IXIARO

Local and Systemic Reactions with 0.25 mL IXIARO (Children Aged <3 Years)

Reaction	Post Dose 1 % (n/N)	Post Dose 2 % (n/N)
Any Injection Site Reaction	20% (1/5)	40% (2/5)
Redness	20% (1/5)	20% (1/5)
Hardening	20% (1/5)	20% (1/5)
Any Systemic Reaction	20% (1/5)	20% (1/5)
Diarrhea	20% (1/5)	20% (1/5)

IXIARO in Traveling Children:
Solicited Local Reactions within 7 Days after 0.5 mL IXIARO

Local Reactions with 0.5 mL IXIARO (Children Aged ≥3 Years)

Reaction	Post Dose 1 (N=55)	Post Dose 2 (N=49)
Any Injection Site Reaction	40%	27%
Tenderness	31%	25%
Pain	18%	16%
Itching	4%	2%
Redness	6%	0
Hardening	0	2%
Swelling	0	0

IXIARO in Traveling Children:
Solicited Systemic Reactions within 7 Days after 0.5 mL IXIARO

Systemic Reactions with 0.5 mL IXIARO (Children Aged ≥3 Years)

Reaction	Post Dose 1 (N=55)	Post Dose 2 (N=49)
Any Systemic Reaction	42%	16%
Muscle pain	27%	2%
Excessive fatigue	13%	0
Fever ≥37.7°C	6%	2%
38.7-39.3 °C	*2%*	*0*
Headache	2%	4%
Rash	2%	2%
Nausea	2%	2%
Diarrhea	2%	0
Loss of appetite	2%	0
Vomiting	0	2%
Irritability	0	6%

IXIARO in Traveling Children:
Summary and Conclusions

- **IXIARO was immunogenic, providing protective antibody titers in both dose groups:**
  - All 51 subjects developed titers above the level of protection (SPR at Day 56: 100%)
  - GMT at Day 56 of 216 with the 0.25 mL and 332 with the 0.5 mL dose
  - At Month 7, for 18 subjects in this interim analysis, titers declined but remained at protective levels

- **IXIARO was generally well tolerated in both dose groups**, with an overall AE profile comparable with adult data for rates of solicited local AE and solicited systemic AE, and lower rates for unsolicited AE.

IXIARO Phase III Pediatric Trial in Endemic Region

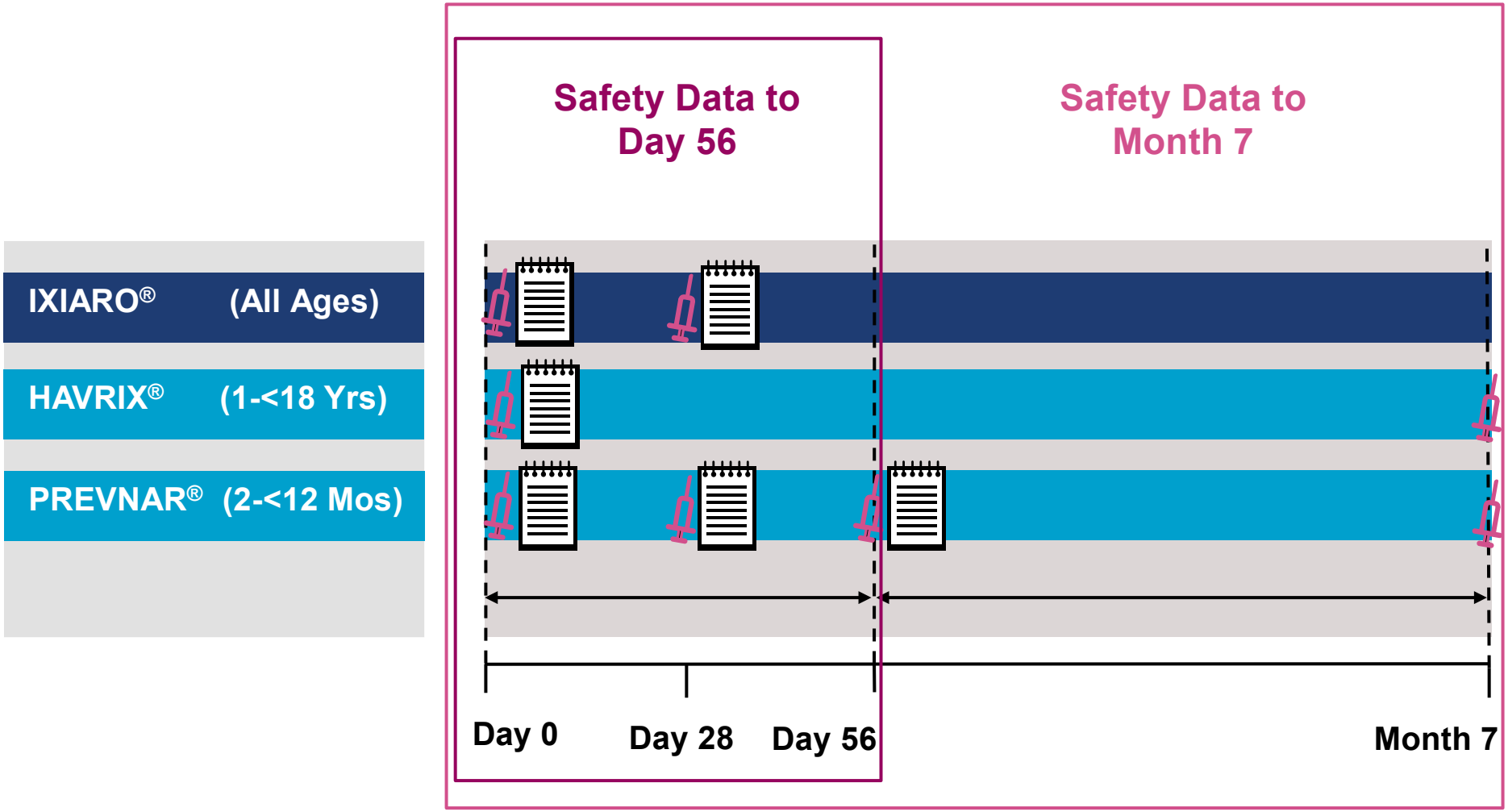
Study Design for Trial IC51-323

Objectives	Safety, Immunogenicity and Dose-confirmation in a JEV Endemic Population
Study Population	1,869 Children / Adolescents; Age Groups ≥2 Months to <18 Years
Design	Open-label, Randomized, Active-controlled Trial
Treatment Groups	IXIARO 0.5 mL, i.m. on Days 0 and 28; N = 540 IXIARO 0.25 mL, i.m. on Days 0 and 28; N = 871 Prevnar®7, 0.5 mL, i.m. on Days 0, (28*), 56 and 3rd/4th dose after study; N = 64 HAVRIX®720 0.5 mL, i.m. on Days 0 and Month 7; N = 394
Follow-up	Day 56 and Month 7 for Immunogenicity and Safety
Countries / Sites	3 Study Sites in the Philippines
Endpoints	Primary Endpoint: Rate of SAE / Medically-attended AEs until Day 56 Immunogenicity (SPR/GMT/fold-increase Rates) at Day 56 and Month 7 Influence of pre-existing JEV and Dengue Antibodies Unsolicited Adverse Events until Day 56 and Month 7 Solicited Adverse Events 7 Days After Each Dose

Prevnar®: 7-valent Pneumococcal Conjugate Vaccine, Wyeth/Pfizer. * Additional dose for 15 children in the Prevnar group aged <6 months at screening
Havrix®720: inactivated Hepatitis A Virus Vaccine, pediatric formulation, GSK

Pediatric Trial in Endemic Region:
Study Scheme

Vaccine Administration and Safety Data Collection (Diaries)



Pediatric Trial in Endemic Region:
Age Distribution of Study Population

Age Group	IXIARO 0.25 mL N=871	IXIARO 0.5 mL N=540	Prevnar N=64	Havrix N=394
2 Months - <1 year	131	-	64	-
1 - <3 years	640	-	-	213
3 - <12 years	100	300	-	101
12 - <18 years	-	240	-	80
Treatment Group Mean Age	2.4	10.6	0.7	6.0

Pediatric Trial in Endemic Region:
Seroprotection after IXIARO

Seroprotection Rate (SPR) by Dose, Intent-to-Treat Population

SPR: Proportion of subjects with a neutralizing antibody titer ≥1:10 by $PRNT_{50}$

	IXIARO 0.25 mL % (n/N)	IXIARO 0.5 mL % (n/N)
Pre-Vaccination	**4.5%** (7/154)	**33.6%** (81/241)
Day 56, 4 Weeks after Dose 2	**99.3%** (147/148)	**100.0%** (237/237)
Month 7, 6 Months after Dose 2	**88.2%** (134/152)	**94.5%** (224/237)

Pediatric Trial in Endemic Region:
Seroconversion after IXIARO

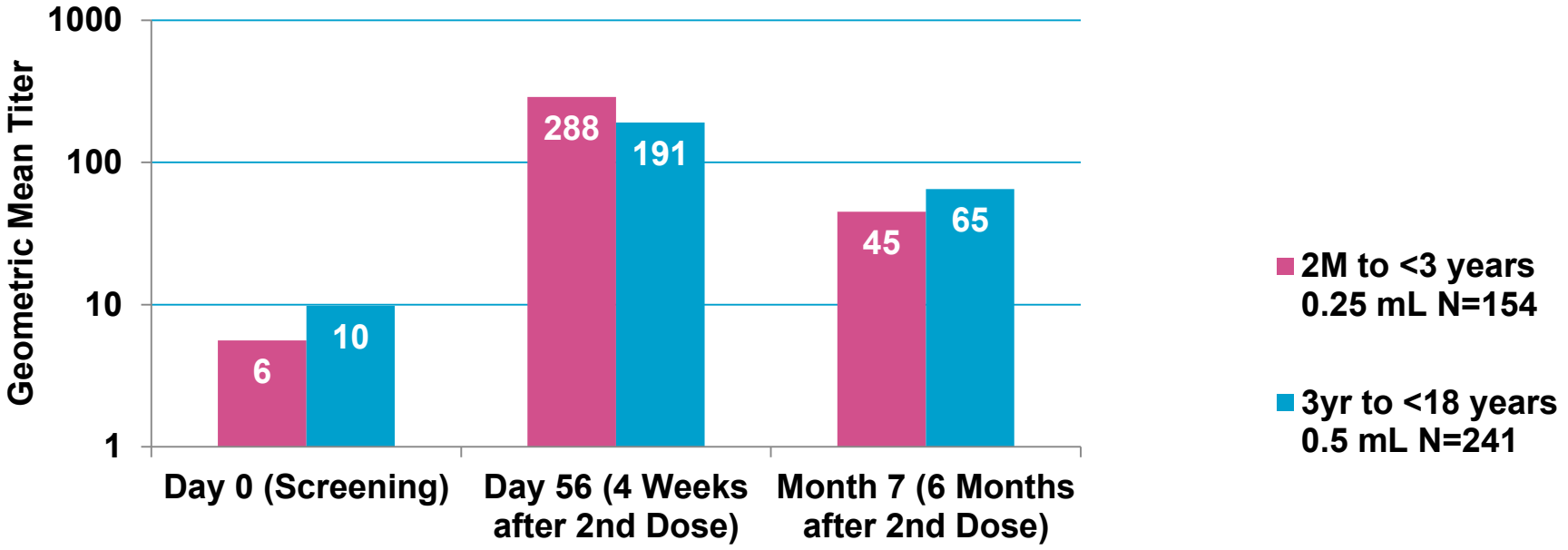
Seroconversion Rates (SCR) by Dose, Intent-to-Treat Population

SCR: Proportion of subjects with **at least four-fold increase in $PRNT_{50}$ titers**

	IXIARO 0.25 mL % (n/N)	**IXIARO 0.5 mL % (n/N)**
Day 56, 4 Weeks after Dose 2	**96.6%** (143/148)	**84.4%** (200/237)

Pediatric Trial in Endemic Region:
Neutralizing Antibodies after IXIARO

GMT for JEV Neutralizing Antibodies by Dose, Intent-To-Treat Population



Pediatric Trial in Endemic Region:
Overview of AE to Day 56
Infants 2 Months to <1 Year

Safety Profile of IXIARO is Comparable to the Control Vaccine Prevnar

Rate of Subjects with	IXIARO 0.25 mL N = 131	Prevnar N = 64
Primary Endpoint: Any SAE/Medically Attended AE	38.2%	42.4%
Any Solicited or Unsolicited AE	84.0%	87.5%
Any Medically Attended AEs	38.2%	42.2%
Any Serious AEs (SAEs)	0	1.6%

Pediatric Trial in Endemic Region:
Overview of AE to Day 56
Children Aged 1 to <18 Years

Safety profile of IXIARO is Comparable to the Control Vaccine Havrix

Rate of Subjects with	IXIARO* N = 1,280	HAVRIX N = 394
Primary Endpoint: Any SAE/Medically Attended AE	16.1%	14.2%
Any Solicited or Unsolicited AE	62.0%	59.6%
Any Medically Attended AEs	16.1%	14.2%
Any Serious AEs (SAEs)	0.5%	1.0%

*** Combined data for 0.25 mL and 0.5 mL dose**

Pediatric Trial in Endemic Region:
Overview of AE to Month 7
Infants 2 Months to <1 Year

Safety Profile of IXIARO Comparable to Prevnar

Rate of Subjects with	IXIARO 0.25 mL N = 131	Prevnar N = 64
Any Solicited or Unsolicited AEs	87.8%	90.6%
Any Medically Attended AEs	48.9%	59.4%
Any Serious AEs (SAEs)	1.5%	1.6%
Any Deaths	0	0

Pediatric Trial in Endemic Region:
Overview of AE to Month 7
Children Aged 1 to <18 Years

Safety Profile of IXIARO Comparable to Havrix

Rate of Subjects with	IXIARO* N = 1,280	HAVRIX N = 394
Any Solicited or Unsolicited AE	70.2%	66.5%
Any Medically Attended AEs	26.3%	25.6%
Any Serious AEs (SAEs)	1.6%	2.5%
Any Deaths	0.1%*	0

*One death, 12 year old male subject:

- Underlying cause of death: disseminated intravascular coagulation following suspected bacterial meningitis and pneumonia
- 4.5 months after the second dose of IXIARO
- Case assessed as unlikely to be attributable to IXIARO by an independent Data Safety Monitoring Board

* Combined data for 0.25 mL and 0.5 mL dose

Pediatric Trial in Endemic Region:
Solicited Local Reactions
Infants <1 Year of Age

Solicited Local Reactions Within 7 Days After Vaccination

	Dose 1		Dose 2	
Reaction	**IXIARO 0.25 mL N = 131**	**Prevnar N = 64**	**IXIARO 0.25 mL N = 131**	**Prevnar N = 64**
Any Injection Site Reaction	19%	32%	8%	18%
Redness	18%	25%	5%	16%
Tenderness	3%	13%	1%	3%
Swelling	2%	6%	2%	2%
Hardening	0	8%	0	2%

Pediatric Trial in Endemic Region:
Solicited Local Reactions
Children 1 to <18 Years of Age

Solicited Local Reactions Within 7 Days After Vaccination

	Dose 1		Dose 2	
Reaction	**IXIARO* N = 1,280**	**Havrix N = 394**	**IXIARO* N = 1,280**	**Havrix N = 394**
Any Injection Site Reaction	14%	14%	6%	Not applicable
Tenderness	5%	6%	2%	
Redness	4%	6%	2%	
Swelling	2%	3%	2%	
Hardening	1%	<1%	<1%	
Pain	8% (62/797)	7% (17/233)	4% (28/794)	
Itching	1% (10/811)	0 (0/242)	<1% (1/814)	

* Combined data for 0.25 mL and 0.5 mL dose

Pediatric Trial in Endemic Region:
Solicited Systemic Reactions
Infants <1 Year of Age

Solicited Systemic Reactions Within 7 Days After Vaccination

	Dose 1		Dose 2	
Reaction	**IXIARO 0.25 mL N = 131**	**Prevnar N = 64**	**IXIARO 0.25 mL N = 131**	**Prevnar N = 64**
Any Solicited Systemic Reaction	36%	40%	23%	31%
Fever ≥37.7°C	24%	25%	15%	23%
≥39.4 – 40.5 °C	*0*	*2%*	*1%*	*2%*
Irritability	15%	13%	8%	8%
Diarrhea	12%	6%	8%	5%
Rash	8%	10%	4%	5%
Vomiting	8%	6%	4%	2%
Loss of appetite	5%	10%	5%	7%
Excessive fatigue	3%	8%	2%	3%

Pediatric Trial in Endemic Region:
Solicited Systemic Reactions
Children 1 to <18 Years of Age

Solicited Systemic Reactions Within 7 Days After Vaccination

	Dose 1		Dose 2	
Reaction	**IXIARO* N = 1,280**	**Havrix N = 394**	**IXIARO* N = 1,280**	**Havrix N = 394**
Any Solicited Systemic Reaction	23%	19%	13%	Not applicable
Fever ≥37.7°C (≥99.9°F)	15%	12%	9%	
≥39.4 – 40.5 °C	*1%*	*1%*	*1%*	
>40.5 °C	*0*	*0*	*<1%*	
Irritability	4%	4%	1%	
Diarrhea	4%	3%	3%	
Loss of appetite	4%	3%	2%	
Vomiting	3%	3%	2%	
Rash	3%	2%	1%	
Excessive fatigue	2%	1%	1%	
Headache	4% (29/765)	5% (10/224)	2% (15/772)	
Flu-like symptoms	3% (27/799)	7% (16/239)	1% (11/804)	
Muscle pain	3% (19/758)	3% (7/221)	1% (6/764)	
Nausea	2% (13/858)	1% (2/257)	1% (4/857)	

* Combined data for 0.25 mL and 0.5 mL dose

Pediatric Trial in Endemic Region:
SAEs to Day 56
Infants 2 Months to <1 Year

No SAEs Occurred up to Day 56 in Children Aged <1 Year Receiving IXIARO

Rate of Subjects with	IXIARO 0.25 mL N = 131 n (%)	*Interval to last IXIARO dose*	Prevnar N = 64 n (%)
Subjects with any SAE	**0**	**-**	**1 (1.6)**
Febrile convulsion	0	-	1 (1.6)

Pediatric Trial in Endemic Region:
SAEs to Day 56
Children Aged 1 to <18 Years

SAEs up to Day 56 Comparable for IXIARO and Havrix

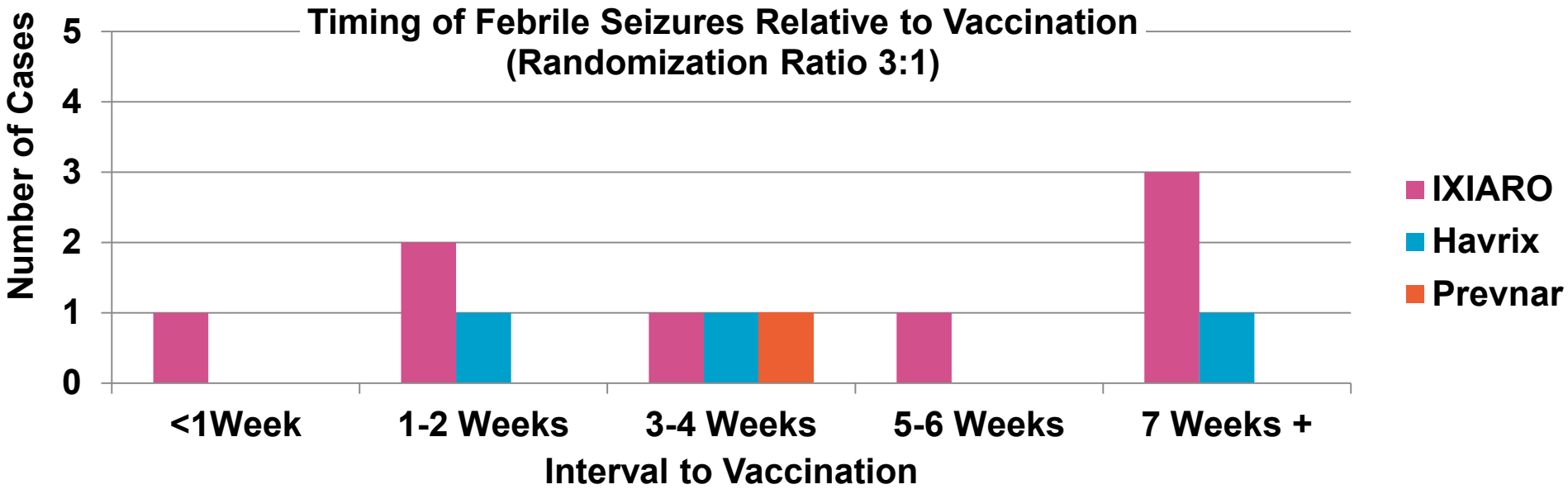
	IXIARO* N=1,280 n (%)	*Interval to last IXIARO dose*	HAVRIX N=394 n (%)
Subjects with any SAE	**6 (0.5)**		**4 (1.0)**
Infections and infestations			
Gastroenteritis	1 (0.1)	*12 Days (1st)*	1 (0.3)
Bronchopneumonia	1 (0.1)	*3 Weeks (2nd)*	0
Cellulitis	1 (0.1)	*9 Days (2nd)*	0
Dengue fever	1 (0.1)	*24 Days (1st)*	0
Other SAEs			
Febrile convulsion	2 (0.2)	*2 Days (2nd); 21 Days (1st)*	2 (0.5)
Dyspnea	0	-	1 (0.3)
Hematoma	1 (0.1)	*12 Days (1st)*	0

* Combined data for 0.25 mL and 0.5 mL dose

Pediatric Trial in Endemic Region:
Febrile Seizures
Children Aged 2 Months to <3 Years

Rate of Febrile Seizures Among Children <3 Years of Age

- IXIARO: 1.0% (8 / 771 children 2 months <3 years)
- Prevnar: 1.6% (1 / 64 children 2 months <1 year)
- Havrix: 1.4% (3 / 213 children 1 year <3 years)



Pediatric Trial in Endemic Region:
Hypersensitivity, Urticaria and Rash within 14 Days after Vaccination

» 9 Subjects with reactions within 14 days after IXIARO (all 0.25 mL dose)
  » **5 of those subjects received a further dose of vaccine without any reaction**

	IXIARO 0.25 mL N=871 n (%)	*Intervals to IXIARO (dose)*	*2nd IXIARO dose given?*	*Reaction to 2nd dose?*	HAVRIX N=394 n (%)
Rash (unsolicited)	3 (0.3)	*7 days (1st)* *8 days (1st)* *10 days (1st)*	*Yes* *Yes* *Yes*	*None* *None* *None*	1 (0.3)
Rash maculo-papular	1 (0.1)	*10 days (2nd)*			0
Rash papular	1 (0.1)	*6 days (2nd)*			0
Hypersensitivity	2 (0.2)	*7 days (2nd)* *11 days (1st)*	*Yes*	*None*	0
Urticaria	2 (0.2)	*5 days (1st)* *13 days (1st)*	*Yes* *No*	*None*	0

Note Differences in Post-Vaccination Observation Time for IXIARO and Controls:

- IXIARO: 2.817 14-person-days post-vaccination
- Prevnar: 141 14-person-days post-vaccination
- Havrix: 394 14-person-days post-vaccination

Pediatric Trial in Endemic Region:
Conclusions

- The safety profile of IXIARO® was comparable to the control vaccines, Prevnar® and Havrix®.
- The most commonly observed AEs were in-line with the expected AE profile in a pediatric population, and mostly were of mild nature.
- The AE profile in the age group 12 to <18 years resembled the solicited AE profile seen in previous adults trials with IXIARO.
- Compared to Prevnar, IXIARO appeared to cause fewer local reactions (tenderness and hardening) in the age group <1 year.
- IXIARO was immunogenic at all age groups tested
  - Seroprotection rate at Day 56 was 99–100%
  - At month 7, Seroprotection Rate ranged between 85.5% and 100%
  - Immunogenicity (GMT) in the age group 12 to <18 years was comparable to levels typically seen in adults after receiving IXIARO

Thank you.

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