Study design and initial data from a Phase 1 randomised controlled observer-blind, trial to evaluate the safety, reactogenicity and immunogenicity of a bivalent vaccine against *Salmonella* Typhi and *Salmonella* Paratyphi A in healthy adults in Europe (NCT05613205)

Usman Nasir Nakakana

Senior Project Physician Lead GSK Vaccines Institute for Global Health

Usman N Nakakana[1], Ilse de Coster[2], Eleanna Sarakinou[1], Marie-Annick Götze[2], Antonella Silvia Scire[1], Giulia Luna Cilio[3], Alimamy Serry-Bangura[3], Iris Sarah De Ryck[3], Martina Carducci[1], Luisa Massai[1], Simona Rondini[1], Valentino Conti[1], Omar Rossi[1], Pierre Van Damme[2] , Ashwani Kumar Arora[1]

[1]GSK Vaccines Institute for Global Health [2]Centre for the Evaluation of Vaccination, University of Antwerp [3]GSK Vaccines Srl, Siena, Italy

Disclosures and funding statement

- UNN, ES, ASC, GLC, ASB, ISDR, MC, LM, SR, VC, OR and AKA are GSK employees. UNN, GLC, ISDR, MC, SR, VC, OR, and AKA hold GSK shares or stock options.
- NVGH (Now GVGH) received grants from Wellcome Trust, and patent on vaccine formulation N425315GB filed.
- IDC acts as principal investigator for vaccine trials conducted on behalf of the University of Antwerp, for which the University obtains research grants from vaccine manufacturers. IDC receives no personal remuneration for this work. ES, M-AG have nothing to declare.

Background

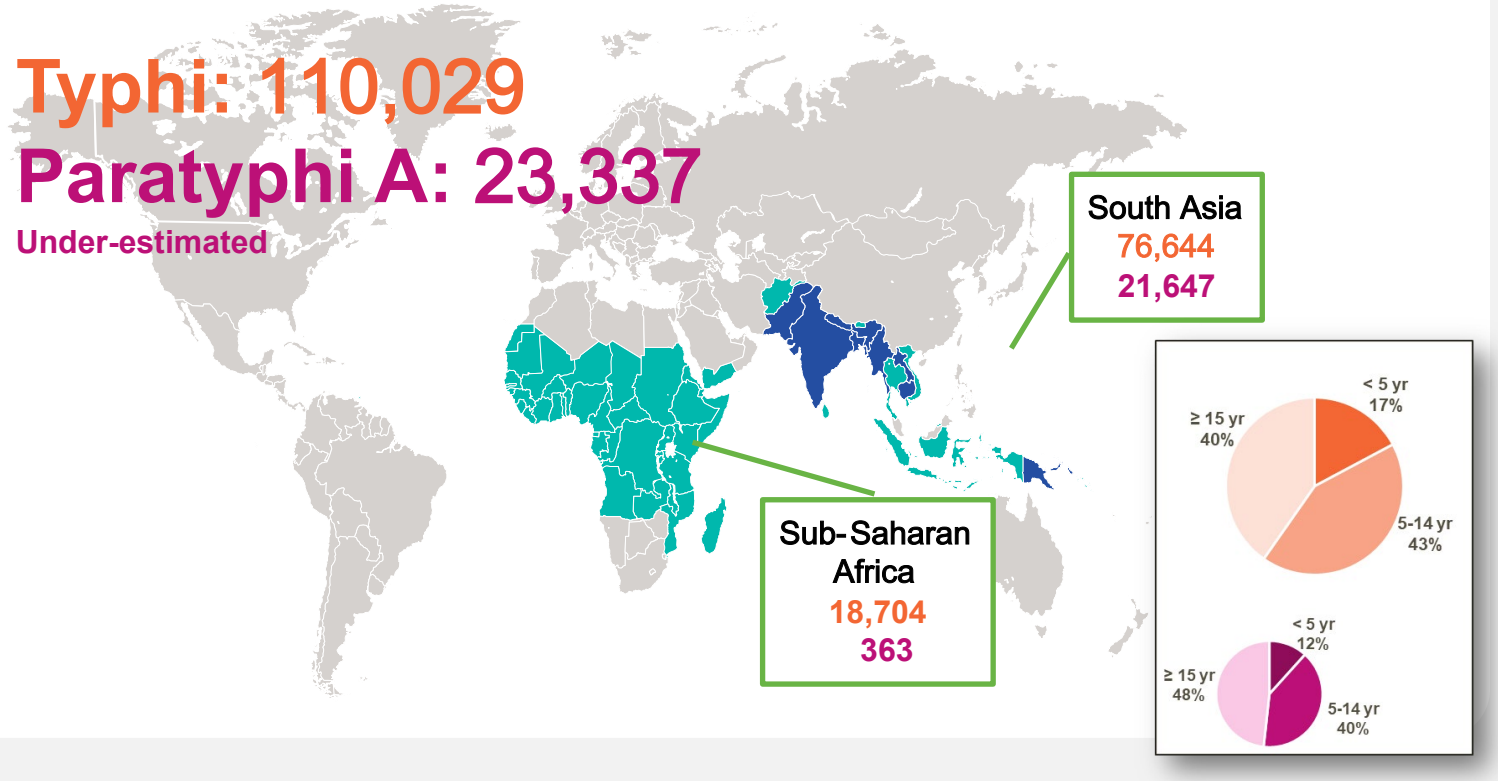
- Despite improved sociosanitary conditions in the last decade, enteric fever remains a major cause of disability and death.
- There is a trend of increased incidence of *S*. Paratyphi A in parts of Asia, estimated as ~35% of cases in India and Nepal and >60% of enteric fever in China, with a similar trend towards rising antimicrobial resistance.
- We present the interim safety results from a first-time-in-human (FTIH) study aimed to evaluate the safety and immunogenicity profile of a novel Typhoid and Paratyphoid A conjugate vaccine (bivalent), aimed to prevent both typhoid and paratyphoid enteric fever in infants and older age groups

Global

Typhi: 110,029

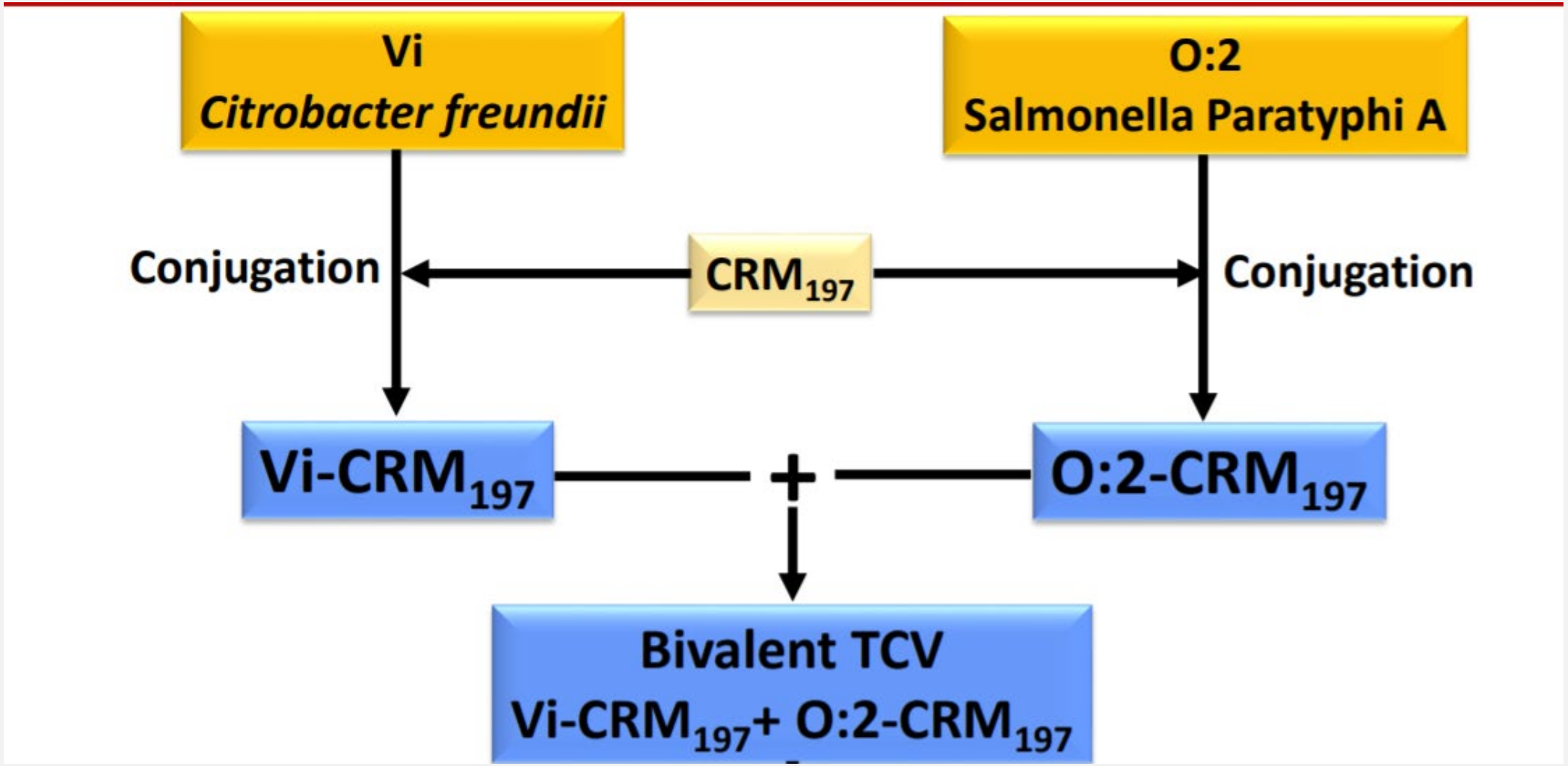
Paratyphi A: 23,337

Under-estimated



GBD IHME website

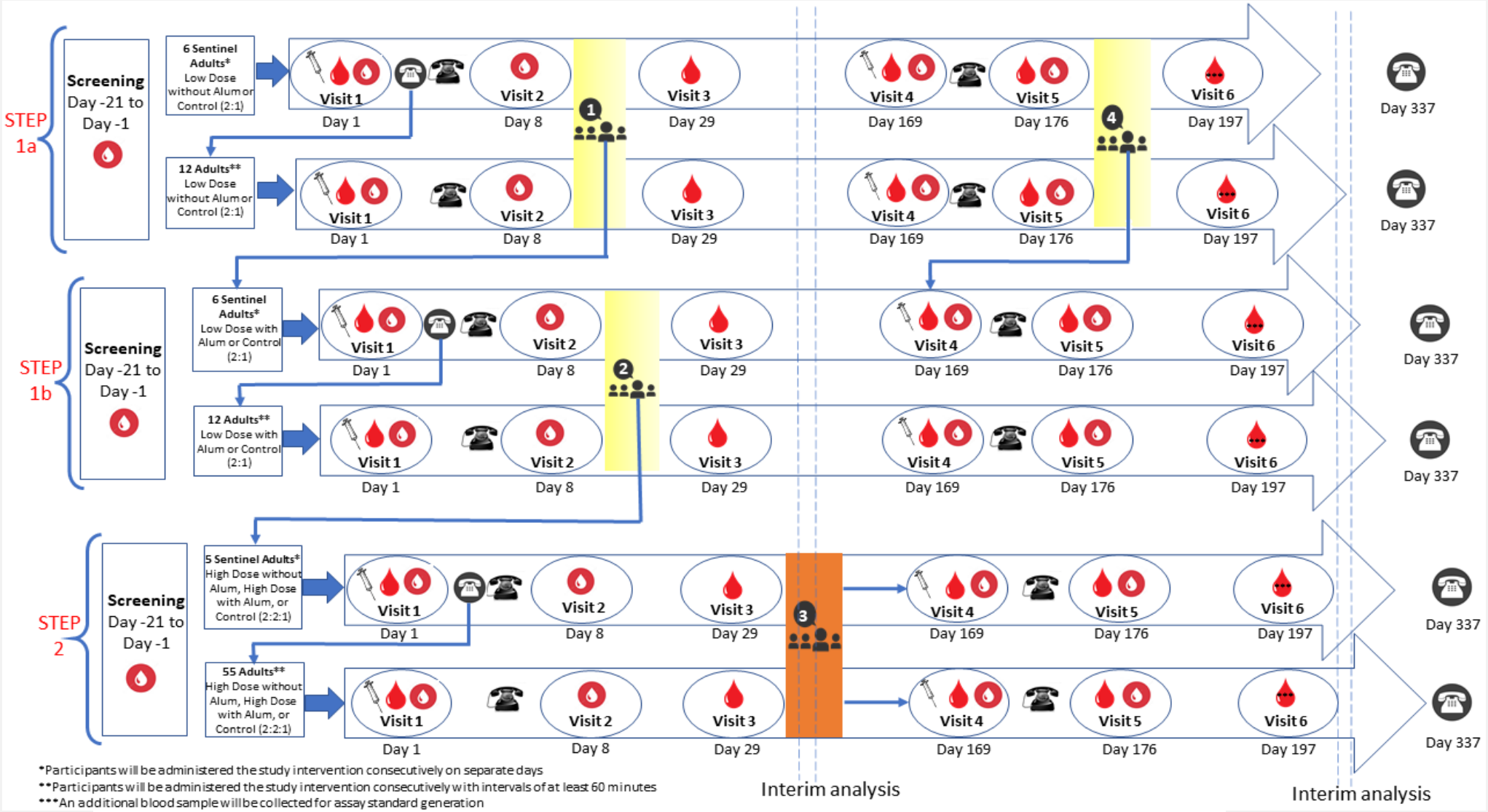
Antigen Description



Summary of study design

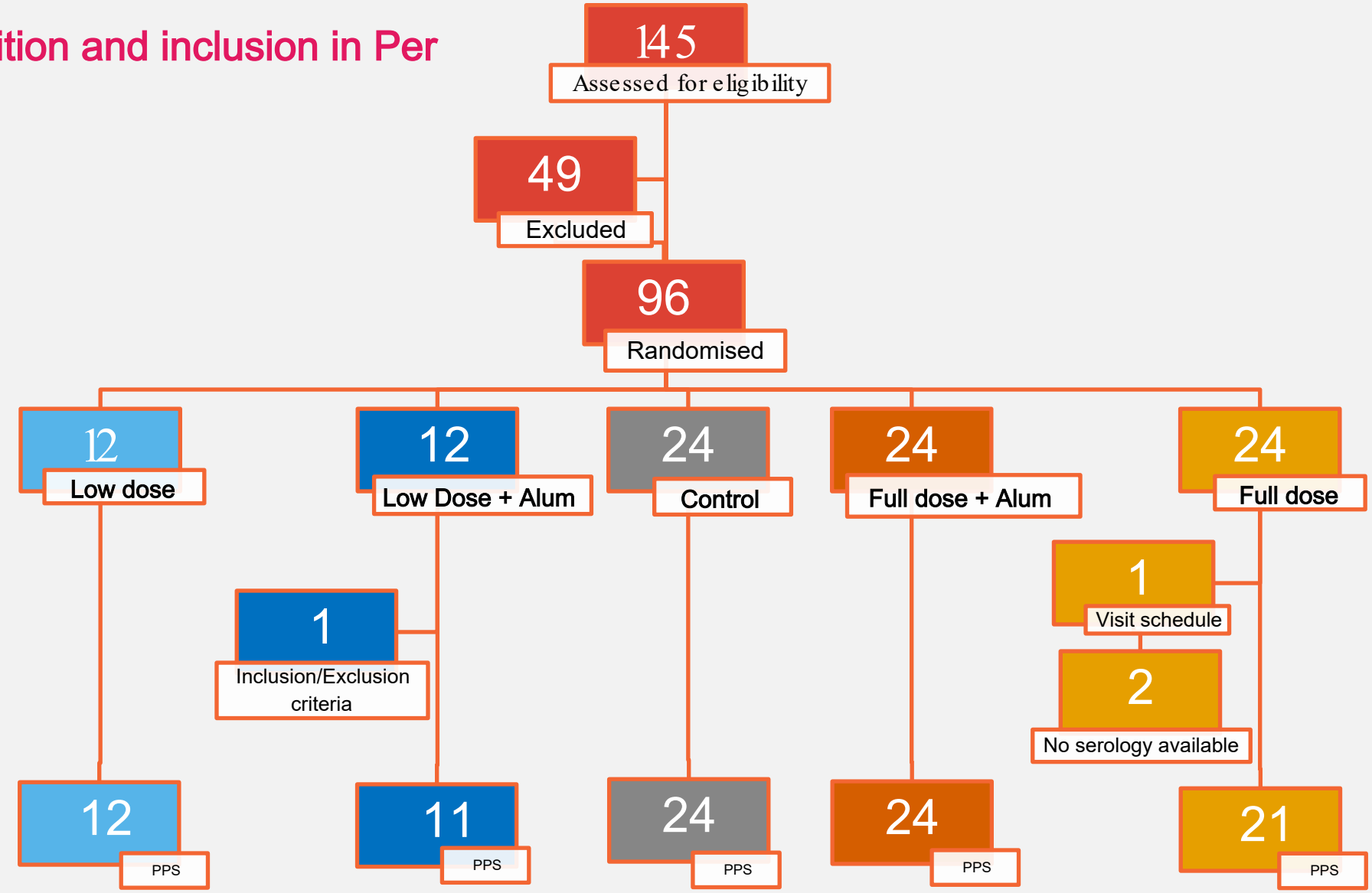
Protocol Title: A Phase I, observer-blind, randomised, controlled, single-centre study to evaluate the safety, reactogenicity, and immune responses to an adjuvanted and non-adjuvanted conjugate vaccine against *Salmonella* Typhi and *Salmonella* Paratyphi A in healthy adults 18 – 50 years of age in Europe		
Rationale for Study:	First time in Human (FIH) Clinical Trial to characterize safety and immunogenicity profile of the candidate vaccine	
Description of study:	96 healthy adults received either a high or lower dose of the candidate bivalent vaccine with or without alum adjuvant or active comparators.	
Primary Objective:	Evaluate the safety profile of the fVi-CRM_{197}+O:2-CRM_{197} vaccine with and without adjuvant	
Secondary Objectives:	1. Evaluate the long-term safety profile of the fVi-CRM_{197}+O:2-CRM_{197} vaccine with and without adjuvant 2. Evaluate the immunogenicity profile of typhoid and paratyphoid A components of fVi-CRM_{197}+O:2-CRM_{197} vaccine with and without adjuvant, using ELISA assay 3. Evaluate the seroresponse rate to the typhoid and paratyphoid A components of the fVi-CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant	
Investigational Products:	• **Two dose levels of Typhi/Paratyphi A vaccine with and without adjuvant are tested in the study:** • 5µg/ 5µg dose **(low dose** – by fractional dosing**)** • 5µg/ 5µg dose with aluminum hydroxide **(low dose adjuvanted** – by fractional dosing**)** • 25µg/ 25µg dose **(full dose)** • 25µg/ 25µg dose with aluminum hydroxide **(full dose adjuvanted)** • **Comparators/Controls:** ➢ Typhim Vi (Typhoid Vi polysaccharide vaccine (Vi-PS vaccine)) ➢ Boostrix (TdaP)	➢ Manufactured by Biological E Ltd. (Bio E, India) ➢ Manufactured by Sanofi Pasteur ➢ Manufactured by GSK

Study Schema



Interim analysis results

Subject disposition and inclusion in Per Protocol Set



Interim analysis results

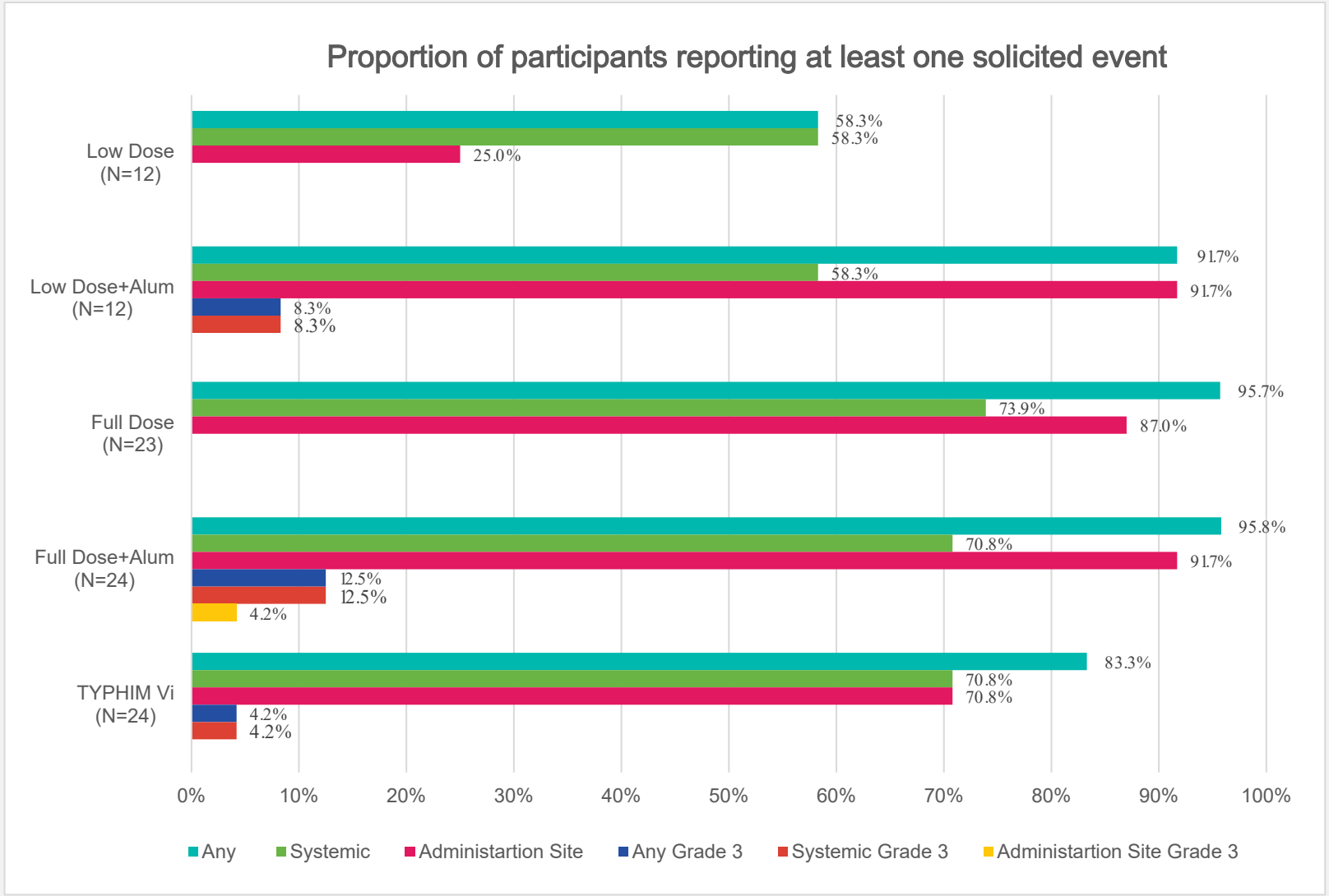
Demographic characteristics of Exposed Population

		Low Dose (N=12)	Low Dose + Alum (N=12)	Full Dose (N=24)	Full Dose + Alum (N=24)	Typhim Vi (N=24)	All Participants (N=96)
Sex							
Male	n (%)	1 (8.3)	6 (50.0)	10 (41.7)	7 (29.2)	6 (25.0)	30 (31.3)
Female	n (%)	11 (91.7)	6 (50.0)	14 (58.3)	17 (70.8)	18 (75.0)	66 (68.8)
Age (years)	n	12	12	24	24	24	96
	Mean	31.9	31.8	27.0	27.1	30.7	29.2
	Minimum	20	20	18	18	18	18
	Maximum	47	49	49	46	50	50
Race							
White	n (%)	12 (100.0)	12 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)	96 (100.0)
Country							
Belgium	n (%)	12 (100.0)	12 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)	96 (100.0)

n / % = number/ percentage of participants in each category; Source: Table 14.1.6

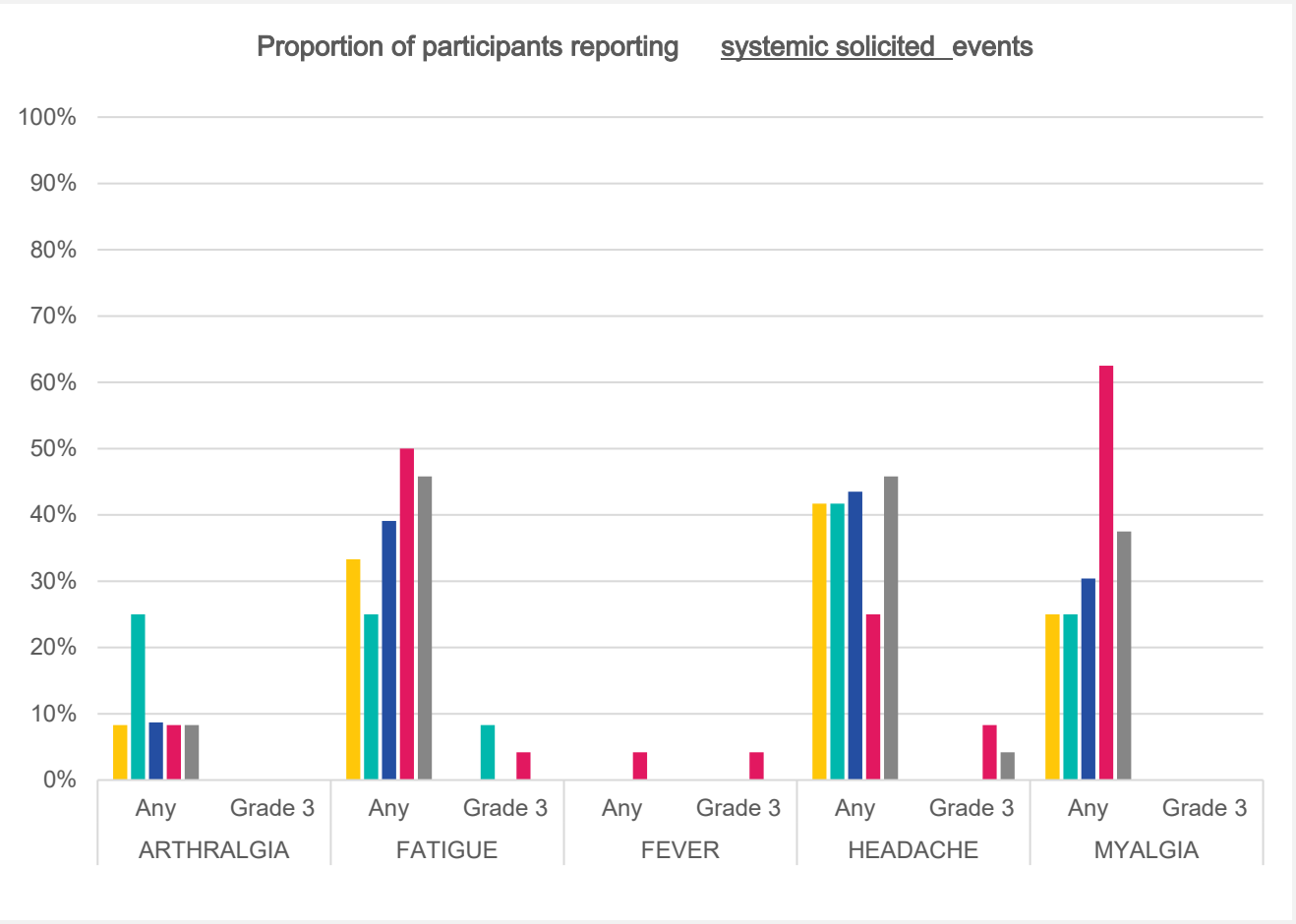
Interim analysis results

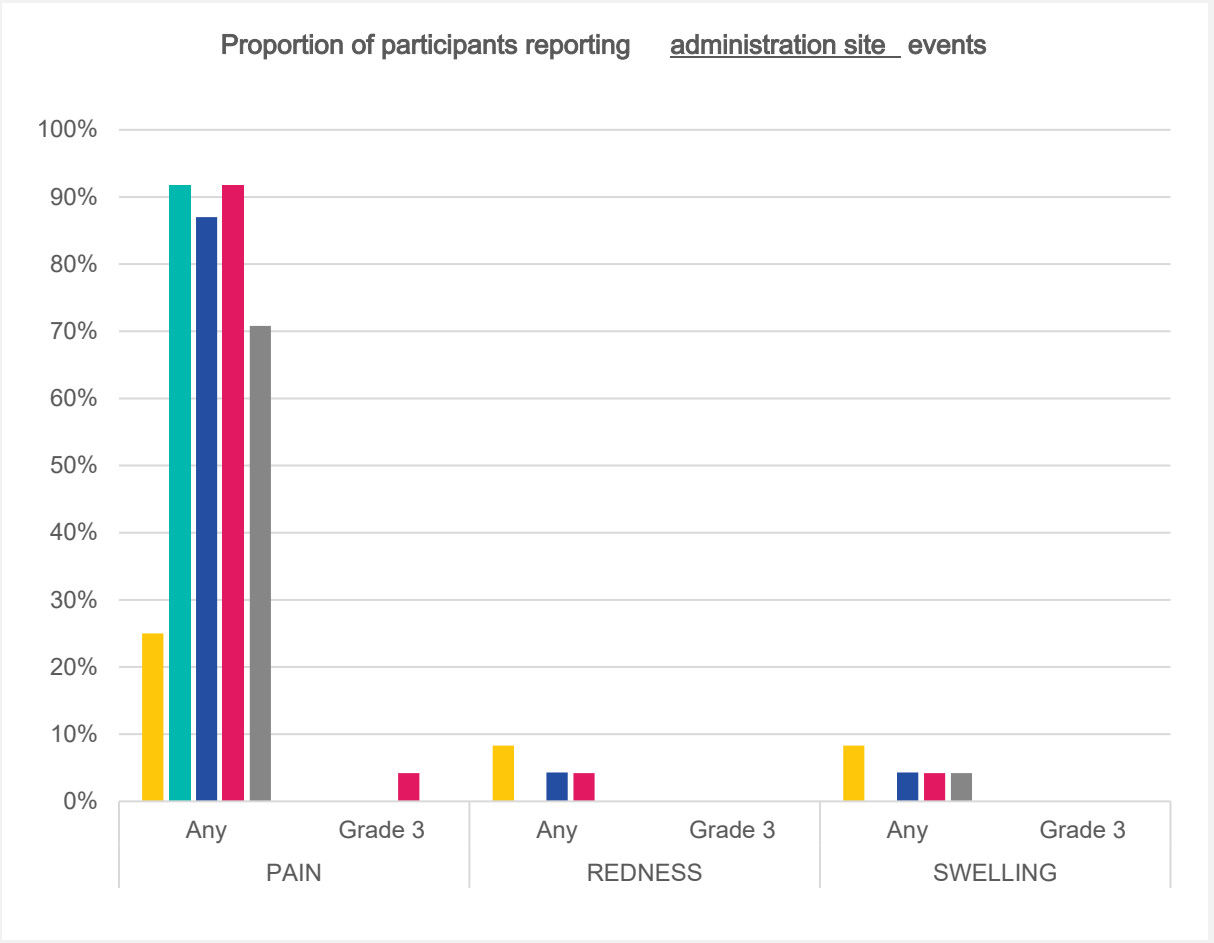
Solicited Events analysis – 7 days post dose 1



Interim Analysis results

Solicited Events analysis – 7 days post dose 1

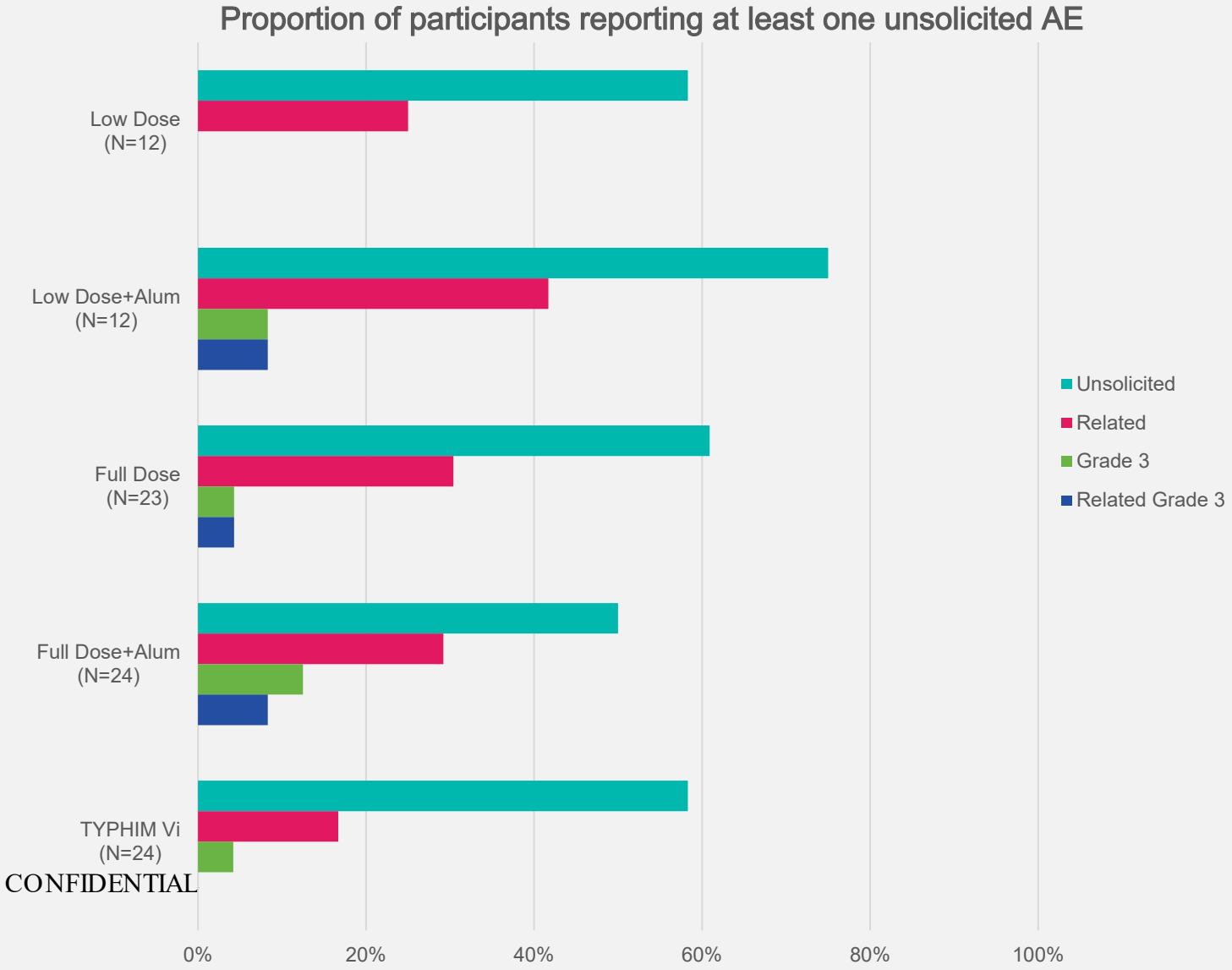




Low Dose (N=12) | Low Dose+Alum (N=12) | Full Dose (N=23) | Full Dose+Alum (N=24) | TYPHIM VI (N=24)

Interim analysis results

Unsolicited Adverse Events analysis –28 days post dose 1



- No Serious Adverse Events (SAEs)
- No Adverse Events (AEs) leading to study/ treatment discontinuation
- No Deaths

Conclusions

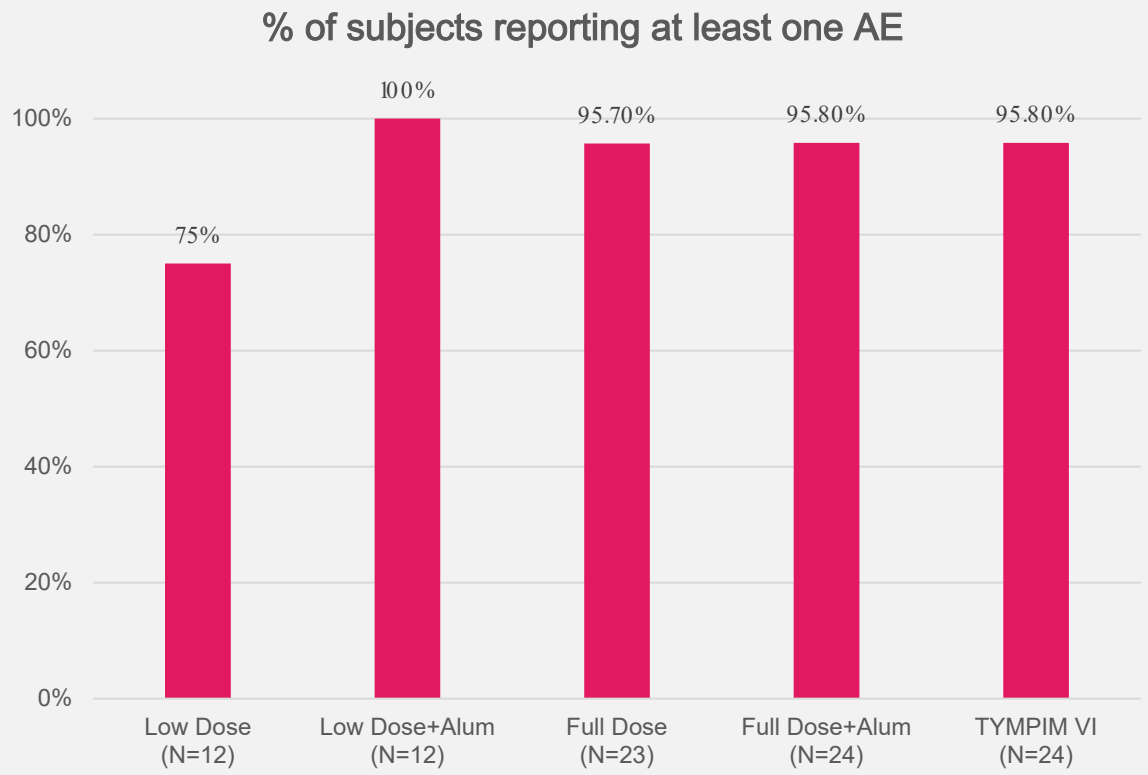
- There were no SAEs, AEs leading to withdrawal from the study or Interventional Product discontinuation up to 28 days after the first study intervention administration in all groups.
- Pain was the most frequently reported solicited administration site event, reported at a similar frequency for all groups except for the Low Dose group without alum which showed a lower frequency. Overall, one grade 3 pain was reported in the Full Dose group with alum.
- Solicited systemic events were reported at a similar frequency for the Full Dose groups and the Control group. There was a higher frequency of grade 3 events (3) in the Full Dose +Alum group.
- Unsolicited AEs were reported with a similar frequency across the groups, with a higher frequency of related severe AEs in the Alum groups (8.3%).

Acknowledgements

- Enteric Fever Project team at GVGH and GSK
- All site staff at Center for Evaluation of Vaccination Belgium
- All study participants and their families

Back up slides

Solicited & Unsolicited Adverse events analysis – 28 days post dose 1



Unsolicited Adverse events analysis –28 days post dose 1

System Organ Class	Blood and lymphatic system disorders	Gastrointestinal disorders	General disorders and administration site conditions	Infections and infestations	Investigations	Musculoskeletal and connective tissue disorders	Nervous system disorders	Reproductive system and breast disorders	Respiratory, thoracic and mediastinal disorders	Skin and subcutaneous tissue disorders	Vascular disorders
Unsolicited Related AEs/Related Grade 3											
Low Dose (N=12)		8.3%	8.3%						8.3%	16.7%	
Low Dose+Alum (N=12)		16.7%	16.7%				8.3%/ **8.3%**	8.3%	8.3%		
Full Dose (N=23)	4.3%	4.3%	13.0%		8.7%/ **4.3%**	13.0%	4.3%			4.3%	
Full Dose+Alum (N=24)			4.2%	4.2%	12.5%/ **8.3%**	4.2%	4.2%				4.2%
TYMPIM VI (N=24)			8.3%				4.2%			4.2%	

Hemoglobin decrease

Migraine

Rate of Concomitant Medication use –28 days post dose 1

	Low dose without alum (%)	Low dose with alum (%)	Full dose without alum (%)	Full dose with alum (%)	Typhim Vi (%)
N	12	12	24	24	24
Any Medication	91.7	75.0	79.2	79.2	83.3
Antipyretic	41.7	41.7	33.3	45.8	66.7
Prophylactic Antipyretic	-	-	-	-	-
Antibiotics	8.3	8.3	-	12.5	8.3

Safety Lab results summary

	Low dose without alum	Low dose with alum	Full dose without alum	Full dose with alum	Typhim Vi
N	12	12	24	24	24
Grade 1 abnormalities	4	3	5	0	0
Grade 1 Hb change from baseline	8	6	14	14	13
Grade 2 Hb change from baseline	0	0	1	0	0
Grade 3 or above Hb change from baseline	0	0	1	2	0

- No other grade 2 abnormalities reported
- No other grade 3 or above abnormalities reported