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A Phase III randomized, double-blind, clinical trial of an investigational hexavalent vaccine given at 2, 4, and 11–12 months

Sven-Arne Silfverdal [a], Giancarlo Icardi [b], Timo Vesikari [c], Sheryl A. Flores [d], Marco F. Pagnoni [d], Jin Xu [d], G. Frank Liu [d], Jon E. Stek [d], Florence Boisnard [e], Stéphane Thomas [e], Eddy Ziani [e], Andrew W. Lee [d,*]

[a] Umeå University, Umeå, Sweden
[b] University of Genoa, IRCCS AOU San Martino, Genoa, Italy
[c] University of Tampere, Tampere, Finland
[d] Merck & Co., Inc., Kenilworth, NJ, United States
[e] Sanofi Pasteur MSD, Lyon, France

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ABSTRACT

Background: Combination vaccines simplify vaccination visits and improve coverage and timeliness. DTaP5-HB-IPV-Hib is a new investigational, fully-liquid, combination vaccine designed to protect against 6 infectious diseases, including 5 pertussis antigens and OMPC instead of PT as conjugated protein for Hib component.

Methods: In this multicenter, double-blind, comparator-controlled, Phase III study (NCT01480258) conducted in Sweden, Italy, and Finland, healthy infants were randomized 1:1 to receive one two immunization regimens. The DTaP5-HB-IPV-Hib Group received the investigational hexavalent vaccine (DTaP5-HB-IPV-Hib) and the Control Group received Infanrix-hexa (DTPa3-HBV-IPV/Hib) at 2, 4 and 11–12 months of age. Both groups received concomitantly Prevnar 13 (PCV13) and Rotateq (RV5) or Rotarix (RV1) at 2, 4 months of age and PCV13 at 11–12 months. Subjects administered RV5 received a 3rd dose at 5 months of age.

Results: A total of 656 subjects were randomized to the DTaP5-HB-IPV-Hib Group and 659 subjects to Control Group. Immune responses to all vaccine antigens post-toddler dose were non-inferior in the DTaP5-HB-IPV-Hib Group as compared to the Control Group. Additionally, the post-dose 2 and pre-toddler DTaP5-HB-IPV-Hib anti-PRP responses were superior. The DTaP5-HB-IPV-Hib Group responses to concomitant RV1 were non-inferior compared to the Control Group.

Solicited adverse event rates after any dose were similar in both groups, except for higher rates of pyrexia (6.4% difference; 95% CI: 1.5,11.3) and somnolence (5.8% difference; 95% CI: 1.7,9.8) in the DTaP5-HB-IPV-Hib Group. Vaccine-related serious adverse events occurred infrequently in the DTaP5-HB-IPV-Hib Group (0.3%) and the Control Group (0.5%).

Conclusions: The safety and immunogenicity of DTaP5-HB-IPV-Hib is generally comparable to Control when administered in the 2, 4, 11–12 month schedule. Early Hib responses were superior versus Control. DTaP5-HB-IPV-Hib could provide a new hexavalent option for pediatric combination vaccines, aligned with recommended immunizations in Europe.

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Abbreviations: AE, adverse event(s); CI, confidence interval; D, diphtheria toxoid; DTaP5, diphtheria, tetanus, acellular pertussis (5-component) vaccine (Daptacel™); DTPa3-HB-IPV/Hib, diphtheria, tetanus, acellular pertussis (3-component), inactivated polio, *Haemophilus influenzae* type b (PRP-T) vaccine (Infanrix™-hexa); DTaP5-HB-IPV-Hib, diphtheria, tetanus, acellular pertussis (5-component), inactivated polio, *Haemophilus influenzae* type b (PRP-OMPC), and hepatitis B vaccine; EU, European Union; FHA, filamentous haemagglutinin; FIM, fimbriae types 2 and 3; GMC, geometric mean concentration; HBsAg, hepatitis B surface antigen; HepB, hepatitis B vaccine (Recombivax HB™); Hib (PRP-OMPC), *Haemophilus influenzae* type b vaccine (polyribosylribitol phosphate-outer membrane protein conjugate) (PedvaxHIB™); Hib (PRP-T), *Haemophilus influenzae* type b vaccine (polyribosylribitol phosphate–tetanus toxoid conjugate) (ActHIB™); IPV, inactivated polio vaccine; PRN, pertactin; PT, pertussis toxoid; PCV13, pneumococcal conjugate vaccine, 13-valent (Prevnar 13™); RV1, rotavirus vaccine, monovalent (Rotarix™); RV5, rotavirus vaccine, 5-valent (RotaTeq™); T, tetanus toxoid.

* Corresponding author at: Merck & Co., Inc., 2000 Galloping Hill Rd., UG-3D063, Kenilworth, NJ 07033, United States.
E-mail address: andrew_wen-tseng_lee@merck.com (A.W. Lee).

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1. Introduction

Vaccination coverage is crucial for meeting the goal of reducing the burden of vaccine-preventable diseases. Combination vaccines offer a practical approach to increase immunization compliance by reducing the number of injections required, simplifying scheduling, and by decreasing pain in children. Combination vaccines have the potential to mitigate these issues and have been shown to improve coverage and timeliness [1–3]. A hexavalent vaccine (Infanrix™-hexa; DTPa3-HBV-IPV/Hib; Control) has been licensed in Europe for over a decade (the only hexavalent vaccine available at the time of the study; this vaccine is not fully liquid and must be reconstituted), a period during which vaccination coverage and compliance with national guidelines improved [4,5]. More recently a liquid hexavalent vaccine with a two-antigen pertussis component (Hexaxim™) has been introduced in Europe and elsewhere [6–9]. This report contains results from a pivotal European Union (EU) Phase III study (NCT01480258) of an investigational hexavalent vaccine (DTaP5-HB-IPV-Hib) containing a five-antigen pertussis component, an outer membrane *Neisseria meningitidis* carrier protein conjugated to the Hib antigen, and a fully liquid formulation. This multicenter, double-blinded study assessed the safety, tolerability, and immunogenicity of DTaP5-HB-IPV-Hib compared to Control, when administered concomitantly with Prevnar 13™ (PCV13) and RotaTeq™ (RV5) or Rotarix™ (RV1) at 2, 4, and 11-to-12 months, representative of the "2 + 1" vaccination schedule employed in several EU countries.

2. Methods

2.1. Population

Healthy infants 46-to-89 days of age were eligible for the study. Participants were excluded if they had (1) participated in another study of an investigational compound or device within 4 weeks of entry, or planned to enroll in another clinical study during the study period; (2) received or expected to receive immunosuppressive agents; (3) received systemic steroids (equivalent of >2 mg/kg total daily dose of prednisone) since birth, any dose within 7 days prior to study entry, or expected to receive steroids through the course of the study; (4) a history of leukemia, lymphoma, malignant melanoma, or myeloproliferative disorder; (5) known or suspected hypersensitivity to any of vaccine component; (6) received any hepatitis B, diphtheria, tetanus, pertussis, pneumococcal, rotavirus (RV5 permitted prior to Visit 1, beginning at 6 weeks of age to subjects in Finland), Hib conjugate, poliovirus vaccines, or combination thereof; (7) a febrile illness, or a rectal temperature $\geqslant$38.0 °C ($\geqslant$100.4°F), within 24 h prior to enrollment; (8) a coagulation disorder contraindicating intramuscular vaccination; (9) a maternal or personal history of HBsAg seropositivity (e.g. chronic hepatitis B); (10) a history of invasive *Haemophilus influenzae* type b (Hib) disease, hepatitis B, diphtheria, tetanus, pertussis, poliomyelitis, rotavirus gastroenteritis, or pneumococcal disease; or (11) any contraindication to the concomitant study vaccines. The protocol was conducted in accordance with principles of Good Clinical Practice (GCP), including obtaining written informed consent from each participant's parent(s) or legal guardian(s) prior to study entry, and was approved by the human studies committees applicable to each study site.

Approximately 650 subjects were be enrolled into each vaccination group. The evaluability was assumed to be 85% at postdose 2 and 80% after the Toddler dose. Thus, the number of evaluable subjects was expected to be approximately 552 per group at postdose 2, and 520 per group after the Toddler dose. The study had a 99% power for the primary acceptability of all DTaP5-HB-IPV-Hib antigens after the Toddler dose.

2.2. Vaccines

Table 1 shows characteristics of the vaccines used in this study. DTaP5-HB-IPV-Hib and PCV13 vaccines were supplied in vials containing 0.5 mL sterile suspension for intramuscular injection. Control was supplied with a lyophilized Hib powder and reconstituted with the liquid DTPa3-HBV-IPV component for intramuscular injection. RV1 and RV5 were supplied as 1.5 mL and 2 mL solution doses, respectively, for oral administration.

All products were prepared, packaged, and labeled in accordance with Good Manufacturing Practice, guidelines for Good Clinical Practice from The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, as well as applicable local laws and regulations. Vaccine supplies were shipped, stored, and distributed in accordance with the study protocol.

2.3. Design

This was a randomized, double-blind, active comparator-controlled study conducted at 23 sites in Italy (DTaP5-HB-IPV-Hib: $n = 132$; Control: $n = 132$), Finland (DTaP5-HB-IPV-Hib: $n = 459$; Control: $n = 460$), and Sweden (DTaP5-HB-IPV-Hib: $n = 65$; Control: $n = 67$) between November 2011 and October

Table 1
Vaccines administered.

Target disease	Antigen	Vaccines[a]	
		Investigational DTaP5-HB-IPV-Hib (Sanofi Pasteur MSD) WL00041213 WL00050254	Licensed DTPa3-HBV-IPV/Hib (GlaxoSmithKline) DL00017089 DL00017092 DL00017411 DL00017986
Diphtheria	D	Not less than 15 Lf	Not less than 25 Lf
Tetanus	T	Not less than 5 Lf	Not less than 10 Lf
Pertussis	PT	20 μg	25 μg
	FHA	20 μg	25 μg
	PRN	3 μg	8 μg
	FIM-2,3[b]	5 μg	
Polio	Type 1 (Mahoney)	40 D-antigen units	40 D-antigen units
	Type 2 (MEF-1)	8 D-antigen units	8 D-antigen units
	Type 3 (Saukett)	32 D-antigen units	32 D-antigen units
Hib	PRP, OMPC	3 μg,50 μg	
	PRP, T		10 μg, 25 μg
Hepatitis B (Adjuvant)	HBsAg	10 μg	10 μg
	Aluminum	0.32 mg	0.82 mg

Abbreviations: D, diphtheria toxoid; FHA, filamentous hemagglutinin; FIM-2,3, fimbriae types 2 and 3; HBsAg, hepatitis B surface antigen; Hib, invasive *H influenzae* disease; HV, investigational hexavalent vaccine; Lf, limit of flocculation units; PRN, pertactin; PRP–OMPC, polyribosylribitol phosphate-*N. meningitidis* serogroup B outer membrane protein conjugate; PRP–T, polyribosylribitol phosphate–tetanus toxoid conjugate; PT, pertussis toxoid; T, tetanus toxoid.

[a] Other licensed vaccines used in the study: RV1 (GSK; lots DL00017328, DL00017452), given as a 1.5 mL oral dose; RV5 (Merck; lots DL00017877, WL00043787), given as a 2.0 mL oral dose; and PCV13 (Pfizer; lots DL00017085, DL00017354, DL00018075), given as a 0.5 mL intramuscular dose.

[b] FIM-2,3 content in DTaP5-HB-IPV-Hib includes both fimbriae 2 and fimbriae 3. Whereas this is counted as 2 antigens, antibody responses to FIM-2 and FIM-3 are not measured separately. Therefore, the immunogenicity text and tables refer to only 4 pertussis antibodies. FIM is not contained in the Control vaccine.