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Study No.: 213503/050 (DTPa-IPV-050)
Title: A phase IIIb, observer-blind, randomized, multicenter, active comparator study to evaluate the safety and immunogenicity of a booster dose of DTPa-IPV/Hib at 18 months of age with GSK Biologicals' DTPa-IPV/Hib compared to Aventis Pasteurs' DTPa-IPV/Hib vaccine (Pentacel™), after an initial primary vaccination series administered at 2, 4, and 6 months of age with Aventis Pasteurs' Pentacel™.
DTPa-IPV/Hib: GlaxoSmithKline Biologicals' diphtheria, tetanus, pertussis, inactivated poliovirus and <i>Haemophilus influenzae</i> type b (Hib); Pentacel™ (Penta): Sanofi Pasteur's (previously Aventis Pasteur) diphtheria, tetanus, pertussis, inactivated poliovirus and <i>Haemophilus influenzae</i> type b (Hib).
Rationale: This study evaluated the serological response to the DTPa-IPV/Hib vaccine compared to Penta vaccine when administered as a 4th dose (booster vaccination) in children primed with 3 doses of Penta.
Phase: IIIb
Study Period: 23 April 2003 to 20 November 2003
Study Design: Observer-blind, randomized, multicenter study with 2 parallel groups with balanced allocation (1:1)
Centers: 5 centers in Canada.
Indication: Immunization against diphtheria, tetanus, pertussis, poliomyelitis and Hib of healthy children.
Treatment: The 2 treatment groups were as follows: <ul style="list-style-type: none"> • DTPa-IPV/Hib group received DTPa-IPV/Hib vaccine, • Penta group received Penta vaccine. Both vaccines were administered intramuscularly into the left deltoid.
Objectives: To demonstrate the non-inferiority of the immune response to diphtheria and tetanus toxoids, acellular pertussis antigens (PT, FHA, PRN), polio and Hib components when DTPa-IPV/Hib was used to boost a three-dose primary series initiated with Penta (i.e. three doses of Penta followed by one dose of DTPa-IPV/Hib) as compared to the immune responses following 4 doses of Penta. The booster was administered at 18 (range 15 to 20) months of age.
Primary Outcome/Efficacy Variable: One month after the booster dose, <ul style="list-style-type: none"> • Seroprotection rates defined as: <ul style="list-style-type: none"> • Percentage of subjects with anti-polyribosyl ribitol phosphate (PRP) antibody concentrations $\geq 1.0 \mu\text{g/mL}$, • Percentage of subjects with anti-diphtheria and anti-tetanus antibody concentrations $\geq 0.1 \text{ IU/mL}$, • Percentage of subjects with anti-poliovirus types 1, 2 and 3 neutralizing antibody titers ≥ 8. • Geometric mean concentrations (GMC) for antibodies against pertussis toxoids (PT), filamentous haemagglutinin (FHA), and pertactin (PRN).
Secondary Outcome/Efficacy Variable(s): <i>Immunogenicity:</i> One month after the booster dose: <ul style="list-style-type: none"> • Percentage of subjects with anti-diphtheria and anti-tetanus toxoid antibody concentrations $\geq 1.0 \text{ IU/mL}$ • Percentage of subjects with anti-PT, FHA and PRN antibody concentrations $\geq 5.0 \text{ EL.U/mL}$ (Seropositivity) • Percentage of subjects with anti-poliovirus types 1, 2 & 3 neutralizing antibody titers ≥ 32 • Booster vaccine response rate to PT, FHA, and PRN, defined as appearance of antibodies in subjects who were initially (i.e. before booster vaccination) seronegative or at least a two-fold increase in antibody concentrations between pre-booster and post-booster vaccination in subjects who were initially seropositive • Geometric mean concentrations or titers (GMCs or GMTs) for antibodies against diphtheria and tetanus toxoids, poliovirus types 1, 2 & 3 and PRP antigen components. <i>Safety:</i> <ul style="list-style-type: none"> • Occurrence of solicited local and general symptoms within 8 days (Day 0-7) after vaccination • Occurrence of unsolicited adverse events (AEs) within 31 days (Day 0-30) after vaccination • Occurrence of serious adverse events (SAEs) during the study period
Statistical Methods: The analyses were performed on the Total Cohort and the According-To-Protocol (ATP) Cohort for immunogenicity. - The Total Cohort included all enrolled subjects who received the booster dose

- The ATP Cohort for analysis of immunogenicity included all subjects meeting all eligibility criteria, complying with the procedures defined in the protocol and for whom data concerning immunogenicity were available.

Immunogenicity analysis:

The analysis was performed on the ATP Cohort for immunogenicity.

Descriptive analysis:

For each time point when blood samples (pre- and post-booster vaccination) were available:

Seroprotection rates for anti-PRP, anti-diphtheria, anti-tetanus antibodies and each of the three poliovirus types 1, 2 and 3 antigens were calculated by group with their exact 95% Confidence Intervals (CIs). Seropositivity rates and vaccine response rates for antibodies against PT, FHA and PRN were calculated by group with exact 95% CIs. GMCs and GMTs for antibodies against each vaccine antigen were calculated by group with their 95% CIs. For GMC and GMT calculations, antibody concentrations or titers below the assay cut-off were given an arbitrary value of half the cut-off

Inferential analysis:

Differences between DTPa-IPV/Hib Group and Penta Group for the seroprotection rates for anti-PRP, anti-diphtheria, anti-tetanus and anti-poliovirus types 1, 2 and 3 antibodies were calculated with the standardized asymptotic 95% CIs. GMC ratios (DTPa-IPV/Hib Group and Penta Group) between the antibody GMCs for anti-PT, anti-FHA and anti-PRN were calculated using an ANCOVA model with the standardized asymptotic 95% CIs. If the lower limit of the standardized asymptotic 95% CI for each rate difference (DTPa-IPV/Hib Group minus Penta Group) was $\geq -10\%$, then non-inferiority for the seroprotection rates was demonstrated. If the lower limit of the 95% CI for the GMC ratios (DTPa-IPV/Hib Group/Penta Group) was ≥ 0.67 , then non-inferiority for the GMC ratio was demonstrated.

Safety analysis:

The analysis of safety was performed on the Total Cohort.

The percentages of subjects with solicited local symptoms (any and Grade 3) and with solicited general symptoms (any, Grade 3 and related) reported during the 8-day (Day 0-7) follow-up period after vaccination were tabulated by group. The percentage of subjects with unsolicited adverse events (AEs) reported during the 31-day (Day 0-30) follow-up period after vaccination was tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. The occurrence of serious adverse events (SAEs) reported during the entire study period was tabulated according to the MedDRA preferred terms.

Study Population: Male or female subjects 18 months of age (range 15 to 20 months), who were presented for a 4th (booster) dose of DTPa-IPV/Hib vaccine. All subjects had documented evidence of priming with 3 doses of Penta in early infancy (starting after 6 weeks of age, separated by at least 6 weeks and completed by 9 months of age, nominally at 2, 4 and 6 months of age) and were free of obvious health problems. Written informed consent was obtained from the parent/ guardian of the subject prior to entry into the study.

Number of Subjects:	DTPa-IPV/Hib Group	Penta Group
Planned, N	220	220
Randomized, N (Total Cohort)	216	217
Completed, n (%)	215 (99.5)	217 (100)
Total Number Subjects Withdrawn, n (%)	1 (0.5)	0 (0.0)
Withdrawn due to Adverse Events, n (%)	0 (0.0)	0 (0.0)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	1 (0.5)	0 (0.0)
Demographics	DTPa-IPV/Hib Group	Penta Group
N (Total Cohort)	216	217
Females:Males	105:111	104:113
Mean Age, months (SD)	16.9 (1.19)	17.2 (1.24)
White, n (%)	200 (92.6)	203 (93.5)

Primary Efficacy Results:

Difference in seroprotection rates between the 2 groups with their standardized asymptotic 95% CIs, one month post-booster (ATP cohort for immunogenicity)

Antibody	DTPa-IPV/Hib		Penta		Difference (DTPa-IPV/Hib - Penta)		
	N	%	N	%	Value (%)	95 % CI	
						LL	UL
Anti-PRP ($\geq 1.0\mu\text{g/mL}$)	197	99.5	187	98.4	1.1	-1.4*	4.2
Anti-Diphtheria ($\geq 0.1\text{IU/mL}$)	198	100	192	100	0.0	-1.9*	2.0
Anti-Tetanus ($\geq 0.1\text{IU/mL}$)	198	100	192	100	0.0	-1.9*	2.0
Anti-poliovirus 1 (≥ 8 dilution)	191	99.5	188	98.9	0.5	-1.9*	3.3

Anti- poliovirus 2 (≥ 8 dilution)	193	100	183	99.5	0.5	-1.4*	3.0						
Anti- poliovirus 3 (≥ 8 dilution)	186	100	178	100	0.0	-2.0*	2.1						
<p>N: number of subjects with available data %: percentage of subjects who were seropositive after the booster dose 95% CI: standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit *Non-inferiority objective met: lower limit of 95% CI on group difference ≥-10% (pre-defined clinical limit for non-inferiority)</p>													
Primary Efficacy Results:													
GMCs ratios between the two groups with their 95% CIs, one month post-booster (ATP cohort for immunogenicity)													
Antibody	DTPa-IPV/Hib			Penta			Adjusted post-booster GMC ratio for DTPa-IPV/Hib / Penta						
	N1	Adjusted post-booster GMC	GM1	N2	Adjusted post-booster GMC	GM2	Value	95 % CI					
								LL	UL				
Anti-PT	179	90.4	19.13	169	66.9	14.16	1.35	1.16*	1.57				
Anti-FHA	189	203.9	15.28	181	133.9	10.03	1.52	1.35*	1.72				
Anti-PRN	191	240.6	17.69	181	172.3	12.67	1.4	1.20*	1.63				
<p>N1: Number of subjects in DTPa-IPV/Hib with both pre-booster and post-booster results available. Adjusted post-booster GMC: predicted GMC post-booster based on an ANCOVA model GM1: Ratio between adjusted post-booster GMC for DTPa-IPV/Hib over the pre-booster GMC across groups N2: Number of subjects in Penta with both pre-booster and post-booster results available. GM2: Ratio between adjusted post-booster GMC for Penta over the pre-booster GMC across groups 95% CI: 95% confidence interval; LL, UL: Lower Limit, Upper Limit *non-inferiority criterion met: lower limit of the 95% CI on the GMC ratio ≥ 0.67 fold (pre-defined clinical limit for non-inferiority)</p>													
Primary Efficacy Results:													
Seroprotection rates and GMCs for anti-PRP antibodies (ATP cohort for immunogenicity)													
Group	Timing	N	≥ 1.0 µg/mL				GMC (µg/mL)						
			n	%	95% CI		value	95% CI					
					LL	UL		LL	UL				
DTPa-IPV/Hib	Pre	189	62	32.8	26.2	40.0	0.687	0.597	0.789				
	P1(M1)*	197	196	99.5	97.2	100	19.062	16.418	22.132				
Penta	Pre	177	47	26.6	20.2	33.7	0.659	0.573	0.759				
	P1(M1)*	187	184	98.4	95.4	99.7	29.037	24.436	34.505				
<p>N: Number of subjects with available results n(%): Number (percentage) of subjects with antibody concentration ≥ the specified cut-off 95% CI: 95% confidence interval; LL: Lower Limit; UL: Upper Limit Pre: Pre-booster blood sample P1(M1): Blood sampling drawn one month after booster vaccination *Primary outcome/efficacy variable</p>													
Primary Efficacy Results:													
Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies (ATP cohort for immunogenicity)													
Group	Timing	N	≥ 0.1 IU/mL				≥ 1.0 IU/mL**				GMC (IU/mL)		
			n	%	95% CI		n	%	95% CI		value	95% CI	
					LL	UL			LL	UL		LL	UL
Anti-Diphtheria													
DTPa-IPV/Hib	Pre	191	160	83.8	77.8	88.7	57	29.8	23.5	36.9	0.435	0.355	0.532
	P1(M1)*	198	198	100	98.2	100	191	96.5	92.9	98.6	5.746	5.058	6.529
Penta	Pre	181	147	81.2	74.8	86.6	51	28.2	21.8	35.3	0.371	0.302	0.454
	P1(M1)*	192	192	100	98.1	100	186	96.9	93.3	98.8	5.859	5.133	6.689
Anti-tetanus													
DTPa-IPV/Hib	Pre	191	184	96.3	92.6	98.5	18	9.4	5.7	14.5	0.358	0.316	0.405
	P1(M1)*	198	198	100	98.2	100	197	99.5	97.2	100	4.656	4.244	5.109
Penta	Pre	181	169	93.4	88.7	96.5	18	9.9	6.0	15.3	0.367	0.322	0.418
	P1(M1)*	192	192	100	98.1	100	190	99.0	96.3	99.9	5.641	5.106	6.233
N: Number of subjects with available results													

n(%): Number (percentage) of subjects with antibody concentration \geq the specified cut-off 95% CI: 95% confidence interval; LL: Lower Limit; UL: Upper Limit Pre: Pre-booster blood sample P1(M1): Blood sampling drawn one month after booster vaccination *Primary outcome/efficacy variable, **Secondary outcome/efficacy variable													
Primary Efficacy Results: Seroprotection rates and GMTs for anti-poliovirus types 1, 2 and 3 antibodies (ATP cohort for immunogenicity)													
Group	Timing	N	≥ 8 Dilution Titer				≥ 32 Dilution Titer**				GMT		
			n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL		LL	UL
Anti-poliovirus type 1													
DTPa-IPV/Hib	Pre	190	135	71.1	64.0	77.4	81	42.6	35.5	50.0	23.2	18.6	28.8
	P1(M1)*	191	190	99.5	97.1	100	188	98.4	95.5	99.7	1293.7	1061.1	1577.4
Penta	Pre	173	127	73.4	66.2	79.8	76	43.9	36.4	51.7	22.9	18.5	28.3
	P1(M1)*	188	186	98.9	96.2	99.9	180	95.7	91.8	98.1	976.2	782.7	1217.6
Anti-poliovirus type 2													
DTPa-IPV/Hib	Pre	188	166	88.3	82.8	92.5	125	66.5	59.3	73.2	44.3	36.4	53.8
	P1(M1)*	193	193	100	98.1	100	193	100	98.1	100	1134.2	964.3	1334.0
Penta	Pre	174	156	89.7	84.1	93.8	110	63.2	55.6	70.4	46.6	37.5	58.0
	P1(M1)*	183	182	99.5	97.0	100	182	99.5	97.0	100	1437.3	1224.2	1687.6
Anti-poliovirus type 3													
DTPa-IPV/Hib	Pre	187	156	83.4	77.3	88.4	112	59.9	52.5	67.0	47.8	37.5	61.0
	P1(M1)*	186	186	100	98.0	100	185	99.5	97.0	100	2118.0	1777.9	2523.1
Penta	Pre	175	140	80.0	73.3	85.7	111	63.4	55.8	70.6	44.2	34.3	56.9
	P1(M1)*	178	178	100	97.9	100	177	99.4	96.9	100	2150.2	1766.7	2616.9
N: Number of subjects with available results n(%): Number (percentage) of subjects with antibody titers \geq the specified cut-off 95% CI: 95% confidence interval; LL: Lower Limit; UL: Upper Limit Pre: Pre-booster blood sample P1(M1): Blood sampling drawn one month after booster vaccination *Primary outcome/efficacy variable, **Secondary outcome/efficacy variable													
Primary Efficacy Results: Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies (ATP cohort for immunogenicity)													
Antibody	Group	Timing	N	≥ 5 EL.U/mL				*GMC (EL.U/mL)					
				n	%	95% CI		value	95% CI				
						LL	UL		LL	UL			
Anti-PT	DTPa-IPV/Hib	Pre	179	77	43.0	35.7	50.6	4.5	4.0	5.1			
		P1(M1)	198	198	100	98.2	100	88.5	79.3	98.7			
	Penta	Pre	169	87	51.5	43.7	59.2	5.0	4.4	5.6			
		P1(M1)	192	192	100	98.1	100	65.6	58.8	73.2			
Anti-FHA	DTPa-IPV/Hib	Pre	191	175	91.6	86.8	95.1	14.3	12.5	16.3			
		P1(M1)	196	196	100	98.1	100	207.3	188.8	227.6			
	Penta	Pre	181	166	91.7	86.7	95.3	12.5	11.0	14.2			
		P1(M1)	192	192	100	98.1	100	132.1	121.2	144.0			
Anti-PRN	DTPa-IPV/Hib	Pre	191	163	85.3	79.5	90.0	14.4	12.3	16.7			
		P1(M1)	198	198	100	98.2	100	251.9	217.2	292.3			
	Penta	Pre	181	155	85.6	79.7	90.4	12.9	11.1	14.9			
		P1(M1)	192	192	100	98.1	100	166.9	145.5	191.4			
N: Number of subjects with available results n(%): Number (percentage) of subjects with antibody concentration ≥ 5 EL.U/ml 95% CI: 95% confidence interval; LL: Lower Limit; UL: Upper Limit Pre: Pre-booster blood sample P1(M1): Blood sampling drawn one month after booster vaccination * Primary result													
Secondary Outcome Variable (s):													

Vaccine response to PT, FHA and PRN antigens, one month after the booster vaccination (ATP cohort for immunogenicity)									
Antibody	Group	Pre-vaccination status	Number of Subjects*	Responders					
				n	%	95% CI			
						LL	UL		
Anti-PT	DTPa-IPV/Hib	S+	77	75	97.4	90.9	99.7		
		S-	102	102	100	96.4	100		
		Total	179	177	98.9	96	99.9		
	Penta	S+	87	85	97.7	91.9	99.7		
		S-	82	82	100	95.6	100		
		Total	169	167	98.8	95.8	99.9		
Anti-FHA	DTPa-IPV/Hib	S+	174	171	98.3	95	99.6		
		S-	15	15	100	78.2	100		
		Total	189	186	98.4	95.4	99.7		
	Penta	S+	166	162	97.6	93.9	99.3		
		S-	15	15	100	78.2	100		
		Total	181	177	97.8	94.4	99.4		
Anti-PRN	DTPa-IPV/Hib	S+	163	158	96.9	93	99		
		S-	28	28	100	87.7	100		
		Total	191	186	97.4	94	99.1		
	Penta	S+	155	152	98.1	94.4	99.6		
		S-	26	26	100	86.8	100		
		Total	181	178	98.3	95.2	99.7		
* : number of subjects with both pre-booster and post-booster results available n(%): Number (percentage) of responders (i.e. subjects who showed a vaccine response to the pertussis antigens) S+/S-: Seropositive/ seronegative subjects at pre-vaccination Total: Subjects who were either seropositive or seronegative at pre-vaccination 95% CI: 95% confidence interval; LL: Lower Limit; UL: Upper Limit									
Secondary Outcome Variable (s):									
Incidence of solicited local symptoms reported during the 8-day (Day 0-7) follow-up period after booster vaccination (Total Cohort)									
Symptom	Intensity	DTPa-IPV/Hib Group (N = 216)				Penta Group (N = 217)			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
Pain	Any	85	39.4	32.8	46.2	113	52.1	45.2	58.9
	Grade 3	3	1.4	0.3	4.0	15	6.9	3.9	11.1
Redness	Any	93	43.1	36.4	49.9	101	46.5	39.8	53.4
	> 50 mm	1	0.5	0.0	2.6	6	2.8	1.0	5.9
Swelling	Any	60	27.8	21.9	34.3	59	27.2	21.4	33.6
	> 50 mm	1	0.5	0.0	2.6	4	1.8	0.5	4.7
N: Number of subjects who received the booster dose n (%): Number (percentage) of subjects presenting at least one type of symptom during the 8-day (Day 0-7) follow-up period after booster vaccination 95% CI: Exact 95% confidence interval; LL: Lower Limit; UL: Upper Limit Any: Any symptom irrespective of intensity grade Grade 3 pain: Cried when limb was moved/ spontaneously painful									
Secondary Outcome Variable (s):									
Incidence of solicited general symptoms reported during the 8-day (Day 0-7) follow-up period after booster vaccination (Total Cohort)									
Group	Intensity/relationship	DTPa-IPV/Hib Group (N = 216)				Penta Group (N = 217)			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
Drowsiness	Any	70	32.4	26.2	39.1	82	37.8	31.3	44.6
	Grade 3	1	0.5	0.0	2.6	5	2.3	0.8	5.3

	Related	68	31.5	25.3	38.1	81	37.3	30.9	44.1
Irritability/ Fussiness	Any	136	63.0	56.1	69.4	136	62.7	55.9	69.1
	Grade 3	8	3.7	1.6	7.2	6	2.8	1.0	5.9
	Related	134	62.0	55.2	68.5	133	61.3	54.5	67.8
Loss of Appetite	Any	86	39.8	33.2	46.7	93	42.9	36.2	49.7
	Grade 3	5	2.3	0.8	5.3	3	1.4	0.3	4.0
	Related	80	37.0	30.6	43.9	89	41.0	34.4	47.9
Fever (Tympanic)	≥38.0°C	27	12.5	8.4	17.7	23	10.6	6.8	15.5
	> 39.5°C	0	0.0	0.0	1.7	2	0.9	0.1	3.3
	Related	28	13.0	8.8	18.2	23	10.6	6.8	15.5

N: Number of subjects who received the booster dose

n (%): Number (percentage) of subjects presenting at least one type of symptom during the 8-day (Day 0-7) follow-up period after booster vaccination

95% CI: Exact 95% confidence interval; LL: Lower Limit; UL: Upper Limit

Any: Any symptom irrespective of intensity grade or relationship to study vaccination

Grade 3 Drowsiness: Drowsiness that prevented normal activity

Grade 3 irritability/fussiness: Crying that could not be comforted and prevented normal activity

Grade 3 loss of appetite: Did not eat at all

Related: Symptoms considered by the investigator to have causal relationship to study vaccination

Safety Results: Number (%) of subjects with unsolicited adverse events (Total Cohort)

Most Frequent Adverse Events - On-Therapy- (occurring within Day 0-30 following vaccination)	DTPa-IPV/Hib Group N = 216	Penta Group N = 217
Subjects with any AE(s), n (%)	127 (58.8)	125 (57.6)
Diarrhea	17 (7.9)	22 (10.1)
Nasopharyngitis	16 (7.4)	22 (10.1)
Upper respiratory tract infection	15 (6.9)	23 (10.6)
Rhinorrhea	10 (4.6)	19 (8.8)
Pyrexia	14 (6.5)	8 (3.7)
Cough	9 (4.2)	8 (3.7)
Vomiting	10 (4.6)	7 (3.2)
Rash	6 (2.8)	9 (4.1)
Teething	9 (4.2)	6 (2.8)
Ear infection	7 (3.2)	6 (2.8)

Safety Results: Number (%) of subjects with Serious Adverse Events (SAEs) (Total Cohort)

Serious adverse event, n (%) [n considered by the investigator to be related to study medication]

All SAEs	DTPa-IPV/Hib Group N = 216	Penta Group N = 217
Subjects with any SAE(s), n (%) [n related]	2 (0.9) [0]	1 (0.5) [0]
Dyspnea	1 (0.5) [0]	1 (0.5) [0]
Bronchiolitis	1 (0.5) [0]	0 (0.0) [0]
Kawasaki's disease	1 (0.5) [0]	0 (0.0) [0]
Lower respiratory tract infection	0 (0.0) [0]	1 (0.5) [0]
Respiratory tract congestion	0 (0.0) [0]	1 (0.5) [0]
Wheezing	0 (0.0) [0]	1 (0.5) [0]
Fatal SAEs	DTPa-IPV/Hib Group N = 216	Penta Group N = 217
Subjects with fatal SAEs, n (%) [related]	0 (0.0) [0]	0 (0.0) [0]

Conclusion: See publication below.

Publications: Halperin S, Tapiero B, Law B, Diaz-Mitoma F, Duval B, Langley JM, Elrick DB, Jacquet J-M. Interchangeability of two diphtheria and tetanus toxoids, acellular pertussis, inactivated poliovirus, Haemophilus influenzae type b conjugate vaccines as a fourth dose in 15–20-month-old toddlers Vaccine 24 (2006) 4017–4023

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