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GENERIC DRUG NAME and/or COMPOUND NUMBER: Bivalent rLP2086 Vaccine / PF-05212366

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not applicable

NATIONAL CLINICAL TRIAL NO.: NCT00798304

PROTOCOL NO.: 6108K2-2000-ES (B1971008)

PROTOCOL TITLE: Single-Blind, Randomized, Phase 1/2 Trial of the Safety, Tolerability, and Immunogenicity of Meningococcal Group B rLP2086 Vaccine in Healthy Infants

The study sponsor is Wyeth, a Pfizer company.

Study Centers: This was a multicenter trial conducted in Spain.

Study Initiation Date and Primary Completion or Completion Dates: 09 January 2009 (First Subject First Visit) to 22 September 2009 (Telephone Contact of Last Subject). The trial was terminated prematurely on 13 January 2011.

Phase of Development: Phase 1/2

Study Objectives:

The primary objective of the study was to assess the immunogenicity of 60 μg, 120 μg, and 200 μg of bivalent rLP2086 as measured by serum bactericidal assay using human complement (hSBA) to meningococcal serogroup B (MnB) strains expressing LP2086 subfamily A and B proteins in healthy infants 1 month after the infant series.

The primary safety objective was to assess the safety and tolerability of 20 μg, 60 μg, 120 μg, and 200 μg of bivalent rLP2086 when given with routine childhood vaccines in healthy infants and toddlers.

The secondary objectives of the study were:

- To assess the immunogenicity of 60 μg, 120 μg, and 200 μg of bivalent rLP2086 as measured by hSBA to MnB strains expressing LP2086 subfamily A and B proteins in healthy toddlers obtained 1 month after the toddler dose.
- To assess the immunogenicity of 60 μg, 120 μg, and 200 μg of bivalent rLP2086, as determined by quantitation of serum immunoglobulin G (IgG) binding to rLP2086

vaccine A and B proteins in healthy infants/toddlers 1 month after the infant series and 1 month after the toddler dose.

The exploratory objectives for Stage 1 of the study were:

- To assess the immune responses induced by licensed routine childhood vaccines when measured 1 month after the infant series. Responses to the following antigens were to be assessed: *Haemophilus influenzae* type b (Hib), pertussis (pertussis toxin, filamentous hemagglutinin, pertactin), inactivated poliomyelitis virus (IPV), hepatitis B virus (HBV)
- To assess the immunogenicity of 20 µg of bivalent rLP2086 as measured by hSBA performed with MnB strains expressing LP2086 subfamily A and B proteins and quantitation of serum immunoglobulin binding to rLP2086 vaccine A and B proteins in healthy infants.

The exploratory objectives for Stage 2 of the study were:

- To assess the immunogenicity of selected dose(s) of bivalent rLP2086 as measured by hSBA to MnB strains expressing LP2086 subfamily A and B proteins in healthy toddlers 6, 12, 18, 24, 36, and 48 months after the toddler dose.
- To assess the immunogenicity of selected dose(s) of bivalent rLP2086 as determined by quantitation of serum IgG to homologous rLP2086 vaccine A and B proteins in healthy toddlers 6, 12, 18, 24, 36, and 48 months after the toddler dose.

Only the safety objectives are addressed in the clinical study report (CSR).

METHODS

Study Design:

This was a phase 1/2, randomized, single-blind (with respect to dosage), multicenter trial in healthy Spanish infants. Subjects were to receive either MnB bivalent rLP2086 plus routine childhood vaccines or routine childhood vaccines only. Doses were to be administered at 2, 4, and 6 months of age (primary infant series) and 12 months of age (toddler dose).

The study was planned to be conducted in 2 stages, where Stage 1 would assess the safety and immunogenicity of the vaccine and provide the basis for dose selection for subsequent studies, and Stage 2 would evaluate the duration of immunity against MnB for up to 4 years after the end of Stage 1. The design of Stage 1 included 2 phases: sentinel and full enrollment. In the sentinel phase, subjects were to be recruited into one of 4 dose-ascending cohorts to receive either a single dose of 20 μg (cohort 1), 60 μg (cohort 2), 120 μg (cohort 3), or 200 μg (cohort 4) of bivalent rLP2086 plus routine childhood vaccines, or routine childhood vaccines only. Enrollment into each cohort was to begin only after review of the 14-day postdose 1 safety data of the preceding cohort. The intention was to assess the safety and immunogenicity of these 4 dose levels, and those not eliminated by the end of the sentinel phase would proceed into the full enrollment phase. In this phase, subjects were to be randomized to receive 3 doses of either one of the selected doses of the bivalent rLP2086 vaccine along with routine childhood vaccines or routine childhood vaccines only. Each subject was to receive the designated vaccine at ages 4, 6, and 12 months, for a total of 4 doses including that given at 2 months in the sentinel phase. The routine vaccinations were to be given based on recommended immunization schedules. The duration of the MnB-specific immune responses was to be assessed by assessing blood samples at 6, 12, 18, 24, 36, and 48 months after the toddler dose.

During enrollment of the 60 μg cohort, a decision was made by the study sponsor to discontinue the trial, with just 46 subjects vaccinated and no immunogenicity data collected. An abbreviated CSR was produced that presents the safety data collected on these 46 subjects.

Number of Subjects (Planned and Analyzed):

A planned 744 subjects were to be enrolled. The Stage 1 sentinel phase was to recruit 198 subjects: those in cohort 1 to receive bivalent rLP2086 vaccine plus routine vaccinations (n=22) or routine childhood vaccines only (n=11), and those in cohorts 2, 3, and 4 to receive bivalent rLP2086 vaccine plus routine vaccinations (n=44 for each cohort) or routine vaccines only (n=11 in each cohort). In the full enrollment phase of Stage 1, up to 546 subjects were to be randomized in a 2:2:2:1 ratio to receive 3 doses of either one of the selected doses of the bivalent rLP2086 vaccine along with routine childhood vaccines (n = up to 156 at each dose level) or routine childhood vaccines only (n = up to 78). When fully enrolled, each of the dosing levels that progressed to full enrollment was to have 200 subjects. However, due to early termination of the trial, the actual number of subjects randomized was just 46: 22 who received 20 μg bivalent rLP2086 (sentinel cohort 1), 10 who received 60 μg bivalent rLP2086 (sentinel cohort 2), and 14 who received routine vaccines only (the pooled control subjects from cohorts 1 and 2).

Diagnosis and Main Criteria for Inclusion:

Subjects were eligible to participate in this study if they were aged 2 months (42 to 98 days) at the time of enrollment and were healthy as determined by medical history, physical examination, and judgment of the investigator. Exclusion criteria included previous vaccination with licensed or investigational products that targeted the same diseases covered by the vaccines used in the study; a previous anaphylactic reaction or other contraindication to any vaccine or vaccine-related component; history of culture-proven invasive disease caused by *Neisseria meningitidis* or *Neisseria gonorrhoea*; and medical conditions that would have precluded participation in the study.

Study Treatment:

The recombinant bivalent vaccine rLP2086 is supplied as a liquid suspension that requires vigorous shaking in a prefilled ready-to-use syringe. The vaccine is administered intramuscularly in the upper quadrant of the anterolateral thigh muscle of the left leg, according to local practice. A 0.5-mL dose contains either 10 µg, 30 µg, 60 µg, or 100 µg of purified rLP2086 proteins from each of the following 2 subfamilies of *N. meningitidis* serogroup B: M98 250771 (subfamily A) and CDC1573 (subfamily B). Inactive ingredients include polysorbate 80 and 0.25 mg of Al^{3+} as AlPO4 in histidine buffer at pH 6.0.

The other planned vaccines were pneumococcal conjugate vaccine (Prevenar), DTaP (diphtheria, tetanus, acellular pertussis)-Hib-HBV+IPV (eg, InfanrixHexa), rotavirus vaccine (RotaTeq or Rotarix), Varicella Vaccine (eg, Varivax), and Measles, Mumps, and Rubella Vaccine (eg, Priorix). In addition to the bivalent rLP2086 vaccine, DTaP-Hib-HBV+IPV and Prevenar vaccines were considered test articles.

Efficacy Evaluations:

No efficacy data were collected in this trial.

Immunogenicity Evaluations:

Due to early termination of the trial, no immunogenicity data were obtained. Details about the planned immunogenicity variables are provided in the study protocol.

Safety Evaluations:

The safety of bivalent rLP2086 vaccine was assessed by monitoring physical examinations, solicited and unsolicited adverse events (AEs), and withdrawals due to AEs.

- A complete medical history and physical examination were performed prior to randomization in order to establish a baseline, and an abbreviated physical examination was planned to be conducted at all other visits except visit 7.

- Parents/legal guardians recorded all solicited reactions (predefined AEs) for 7 days after vaccination in an electronic diary (e-diary):

    - Solicited local reactions were measured at the rLP2086 injection site for rLP2086 recipients and at the Prevenar injection site for control subjects. For redness and swelling, parents/legal guardians were to measure and record the largest diameter,

since the previous entry, of any reactions, and categorize them as absent, mild (0.5 to 2.0 cm), moderate (2.5 to 7.0 cm), or severe (>7.0 cm). For tenderness, they were asked to record whether there was no discernible tenderness, tenderness present (cried or protested only when touched at injection site), or tenderness interfered with limb movement (cried and protested to limb movement).

- The solicited systemic events collected were fever (temperature ≥38°C), irritability, increased sleep, decreased sleep, and decreased appetite, as well as the use of antipyretic medication to treat and prevent symptoms. Temperature was categorized as absent (<38.0ºC), mild ≥38.0°C to ≤39.0°C), moderate (>39.0°C to ≤40.0°C), or severe (>40.0°C).

- Any AEs other than solicited local reactions and systemic events were considered unsolicited AEs. AEs were to be collected from the signing of the informed consent form (ICF) through visit 5, and from visit 6 to 7 days after visit 7.

- Serious AEs (SAEs) were to be collected throughout the study. For Stage 1 of the study, all SAEs were to be collected from the signing of the ICF to 7 days after visit 7. For Stage 2, SAEs were to be collected and reported for 7 days after each blood draw.

Statistical Methods:
The safety analysis included all subjects who received at least 1 dose. Control groups were combined into 1 group. Safety data were summarized using descriptive statistics throughout the study. No type I error was spent on these descriptive analyses.

Reactogenicity (local reactions and systemic events) was evaluated by summarizing the number of subjects reporting each reaction or event, by vaccine group and dose, using descriptive statistics. Severity of local reactions was also summarized, using descriptive statistics by vaccine group and dose.

AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA), and were summarized by vaccine group. All summaries showed the number and percentage of subjects experiencing at least 1 event. Additional summaries by AE severity and vaccine relation were produced.

RESULTS

Subject Disposition and Demography:

Disposition is presented in Table 1. The planned enrollment was up to 744 subjects. However, due to early study termination, the actual number of subjects randomized was just 46: 22 to receive 20 µg bivalent rLP2086 (sentinel cohort 1), 10 to receive 60 µg bivalent rLP2086 (sentinel cohort 2), and 14 to receive routine vaccines only (the pooled control subjects from cohorts 1 and 2). All randomized subjects were vaccinated and were included in the safety analysis population. Prior to the study being terminated, 2 subjects were withdrawn due to adverse events: 1 in the 20 µg group due to a urinary tract infection, and 1 in the 60 µg group due to aseptic meningitis. Neither event was deemed related to vaccination. The remaining 44 subjects were all withdrawn when the trial was terminated.

Table 1. Disposition of Subjects

	Vaccine Group (as Administered)			
	Control (n=14)	20 µg rLP2086 (n=22)	60 µg rLP2086 (n=10)	Total (n=46)
Randomized	14 (100.0)	22 (100.0)	10 (100.0)	46 (100.0)
Vaccinated				
Vaccination 1	14 (100.0)	22 (100.0)	10 (100.0)	46 (100.0)
Completed	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawn	14 (100.0)	22 (100.0)	10 (100.0)	46 (100.0)
Reasons for Withdrawal				
Adverse Event	0 (0.0)	1 (4.5)	1 (10.0)	2 (4.3)
Discontinuation of Cohort by Sponsor	14 (100.0)	21 (95.5)	9 (90.0)	44 (95.7)

The study population consisted of 46 healthy infants aged 45 to 86 days at enrollment, with a mean age of 65.5 days. Approximately half the subjects were female (22 of 46). All subjects were white.

Immunogenicity Results:

As the study was terminated prior to the first scheduled post-vaccination blood draw, no immunogenicity data are available.

Safety Results:

All 46 randomized subjects received 1 dose of study vaccine and were included in all safety evaluations. Because of the early termination of the trial, no subject received more than 1 dose of study vaccine; therefore, all safety data are for dose 1 only.

Local Reactions:

At least 1 local reaction of any type was reported for 11 (50.0%) subjects in the 20 μg group, for 7 (70.0%) subjects in the 60 μg group, and for 5 (35.7%) subjects in the control group. With the exception of erythema, the rate of all reactions was lowest in the control group and highest in the 60 μg group. The most common local reaction was tenderness, with tenderness of any severity reported for 8 (36.4%) subjects in the 20 μg group, 7 (70.0%) subjects in the 60 μg group, and 2 (14.3%) subjects in the control group. Induration of any severity was reported for 4 (18.2%), 3 (30.0%), and 2 (14.3%) subjects, respectively; and erythema was reported for 6 (27.3%), 3 (30.0%), and 4 (28.6%) subjects, respectively. One subject (4.5%) in the 20 μg group and 4 subjects (40.0%) in the 60 μg group experienced tenderness of a severity that interfered with limb movement. For induration, most cases were mild, with moderate reactions experienced by 3 subjects (13.6%) in the 20 μg group and by 1 (10.0%) in the 60 μg group. For erythema, all cases were mild with the exception of a moderate reaction in 1 subject (4.5%) in the 20 μg dose group. The mean duration of tenderness was 1.3 days in the 20 μg group, 2.7 days in the 60 μg group, and 1.0 day in the control group; that for induration was 4.3, 3.3, and 4.5 days, respectively; and that for erythema was 1.0, 1.7, and 1.3 days, respectively.

Systemic Events:

At least 1 systemic event of any type was reported for 21 (95.5%) subjects in the 20 μg group; for all 10 (100%) subjects in the 60 μg group; and for 12 (85.7%) subjects in the control group. The most common event was irritability, reported for 17 (77.3%), 9 (90.0%), and 9 (64.3%) subjects, respectively. Rates of the other reactions were consistently lowest in the control group and highest in the 60 μg group, with the exception of decreased sleep for which no occurrences were reported in the 60 μg group. Duration of events ranged from 1.0 day (decreased sleep in the control group) to 3.3 days (increased sleep in the 60 μg group). Duration in the control group was consistently lowest, but there was not a clear trend for the 2 bivalent rLP2086 vaccine groups, with slightly longer durations in the 20 μg group for irritability (3.2 vs 2.7 days), and slightly longer durations in the 60 μg group for decreased appetite (2.3 vs 2.2 days) and increased sleep (3.3 vs 2.0 days). Systemic events were not graded for severity. The rate of use anti-pyretic medication for either the prevention or the treatment of symptoms was consistently lowest in the control group and highest in the 60 μg group. Duration of medication use followed the trend of being lowest in the control group and highest in the 60 μg group, ranging overall from 1.0 to 2.5 days.

Fever:
Fever in any category was reported in the majority of bivalent rLP2086 vaccine recipients: 14 (63.6%) in the 20 μg group and 8 (80.0%) in the 60 μg group, compared to 4 (28.6%) in the control group. In most cases, the temperature was 38.0–39.0°C, but 2 subjects in the 20 μg group and 1 in the 60 μg group had fever of 39.1–40.0°C. (Note that these data do not count a fever in the child with aseptic meningitis because it was not recorded in the e-diary.) There were no reported occurrences of fever >40.0°C. The mean duration of fever was 2.1 days in the 20 μg group, 1.9 days in the 60 μg group, and 1.0 day in the control group.

Unsolicited Adverse Events:

A total of 18 AEs were reported for 12 subjects: 7 in the 20 µg group, 2 in the 60 µg group, and 3 in the control group. Most of the AEs were related to infection (eg, respiratory, viral, and urinary tract infections), which is typical of the population enrolled in the study. Overall, the majority of AEs were in the system organ class of infections and infestations: 9 of 11 AEs in the 20 µg group; 2 of 3 AEs in the 60 µg group; and 2 of 5 AEs in the control group. The only individual AE reported in more than 1 subject was viral infection (2 subjects in the 20 µg group). See Table 2.

Table 2. Adverse Events

System Organ Class[a] Preferred Term	Vaccine Group (as Administered)								
	Control n=14			20 µg rLP2086 n=22			60 µg rLP2086 n=10		
	No. of Subjects[b]	%	No. of Episodes[c]	No. of Subjects[b]	%	No. of Episodes[c]	No. of Subjects[b]	%	No. of Episodes[c]
Any Adverse Event	3	(21.4)	5	7	(31.8)	11	2	(20.0)	3
Eye disorders	1	(7.1)	1	0		0	0		0
Conjunctivitis	1	(7.1)	1	0		0	0		0
Gastrointestinal disorders	0		0	1	(4.5)	1	1	(10.0)	1
Gastrooesophageal reflux disease	0		0	1	(4.5)	1	1	(10.0)	1
Infections and infestations	2	(14.3)	2	6	(27.3)	9	1	(10.0)	2
Bronchitis	0		0	1	(4.5)	2	0		0
Gastroenteritis	0		0	1	(4.5)	1	0		0
Meningitis aseptic	0		0	0		0	1	(10.0)	1
Nasopharyngitis	0		0	0		0	1	(10.0)	1
Respiratory syncytial virus bronchiolitis	0		0	1	(4.5)	1	0		0
Respiratory tract infection	1	(7.1)	1	1	(4.5)	1	0		0
Respiratory tract infection viral	1	(7.1)	1	0		0	0		0
Urinary tract infection	0		0	2	(9.1)	2	0		0
Viral infection	0		0	2	(9.1)	2	0		0
Respiratory, thoracic and mediastinal disorders	1	(7.1)	1	0		0	0		0
Asthma	1	(7.1)	1	0		0	0		0
Skin and subcutaneous tissue disorders	1	(7.1)	1	1	(4.5)	1	0		0
Dermatitis	1	(7.1)	1	0		0	0		0
Rash	0		0	1	(4.5)	1	0		0

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.
b. The number of subjects reporting at least 1 episode of the event specified. For 'Any Adverse Event,' it represents the number of subjects reporting at least 1 episode of any kind of event.
c. The total number of episodes of the event specified. Subjects can be represented more than once. 'Any Adverse Event' and 'By System Organ Class' counts are the sum of individual episodes within that category.
n=number of subjects; No.=number

Safety-Related Discontinuations:

Before enrollment in the study was terminated, 2 subjects, 1 in each of the bivalent rLP2086 vaccine groups, were withdrawn from the study because of AEs: 1 case of aseptic meningitis and 1 case of urinary tract infection. Both AEs were deemed not related to vaccination. See Table 3.

Table 3. Listing of Subjects Withdrawn Due to Adverse Events

Site	Cohort	Subject	Event Description	Vaccine Administered	Dose	Days Since Last Dose	Duration (Days)	Severity	Related[a]	Outcome
61082000008	2	000356	Meningitis aseptic	60 µg rLP2086	1	2	8	Moderate	No	Resolved
61082000012	1	000558	Urinary tract infection	20 µg rLP2086	1	9	8	Moderate	No	Resolved

a. Based on investigator assessment.
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Serious Adverse Events/Deaths:

There were no deaths in the study. A total of 7 SAEs were reported by 5 subjects: 4 subjects in the 20 µg group, with bronchitis (2 cases in the same subject), urinary tract infection (2 cases), viral infection, and respiratory syncytial virus bronchiolitis; and 1 subject in the 60 µg group, with aseptic meningitis. None were deemed to be related to vaccination. All the children recovered. Two of the SAEs led to discontinuation from the trial. See Table 4.

Table 4. Serious Adverse Events

Site	Cohort	Subject	Event Description	Vaccine Administered	Dose	Days Since Last Dose	Duration (Days)	Severity	Related[a]	Outcome
61082000008	1	000355	Bronchitis	20 µg rLP2086	1	65	8	Severe	No	Resolved
	1		Bronchitis	20 µg rLP2086		90	7	Severe	No	Resolved
	2	000356	Meningitis aseptic	60 µg rLP2086	1	2	8	Moderate	No	Resolved
61082000012	1	000558	Urinary tract infection	20 µg rLP2086	1	9	8	Moderate	No	Resolved
	1	000559	Urinary tract infection	20 µg rLP2086	1	136	5	Mild	No	Resolved
	1		Viral infection	20 µg rLP2086		9	6	Moderate	No	Resolved
61082000013	1	000601	Respiratory syncytial virus bronchiolitis	20 µg rLP2086	1	12	8	Moderate	No	Resolved

a. Based on investigator assessment.

CONCLUSIONS:

Based upon phase 1 safety and immunogenicity data with toddlers, adolescents, and adults, dose levels of 20, 60, 120 and 200 μg bivalent rLP2086 vaccine were initially chosen for this study.

The safety conclusions based on 1 dose of 20 μg or 60 μg bivalent rLP2086 vaccine administered in infants are as follows:

- Local reactions were generally mild or moderate in severity. There were no cases of severe induration or erythema. Tenderness that interfered with limb movement was reported for 5 subjects: 1 in the 20 μg bivalent rLP2086 group (4.5%) and 4 in the 60 μg bivalent rLP2086 group (40%).
- Irritability was the most common systemic event. Systemic reactions were generally more frequent in the bivalent rLP2086 groups than in the control group (routine childhood vaccines only).
- AEs were infrequent, and most were infection-related (eg, respiratory, viral, and urinary tract infections), which is typical of the population enrolled in the study.
- Fever was more frequent in the bivalent rLP2086 groups than in the control group, seen in 63.6% of subjects in the 20 μg group and 80.0% of subjects in the 60 μg group (90.0% if the case of aseptic meningitis is included), compared with 28.6% in the control group. Most fevers were ≤39.0°C; 2 subjects in the 20 μg group and 1 subject in the 60 μg group had fever 39.1–40.0°C. There were no reported cases of fever >40.0°C.

Per protocol, a Project-Independent Safety Review Team (PISRT) was in place to review the 14-day post-vaccination safety data at the completion of each sentinel dose cohort and to perform an ad hoc safety evaluation in the case that protocol stopping rules were met. After 22 subjects received 20 μg bivalent rLP2986 vaccine within sentinel cohort 1, the PISRT judged the tolerability of 20 μg bivalent rLP2086 vaccine after dose 1 to be reasonable with 23% of the subjects experiencing mild to moderate swelling, 36% experiencing mild to moderate redness. Twelve subjects experienced mild fevers and 2 subjects developed moderate fever. The local reactogenicity rates were comparable to a previous phase 1 toddler study and the decision was made to proceed with the next sentinel cohort. After 10 subjects received the 60 μg bivalent rLP2086 vaccine, a subject developed aseptic meningitis that was initially thought to be causally related to the vaccine. This triggered a protocol-defined pause (no more infants could be enrolled) and an evaluation of all cumulative safety data post dose 1 at the 20 and 60 μg dose levels by the PISRT. The aseptic meningitis case was ultimately judged to be not related to the vaccine by the investigator. Review of cumulative safety data by the PISRT revealed that at the 60 μg dose level, 9 out of 10 bivalent rLP2086 vaccine recipients experienced mild to moderate fever (only 1 subject had moderate fever). Rates for local reactogenicity were similar to the 20 μg dose level, with 30% of bivalent rLP2086 vaccine recipients experiencing mild to moderate swelling or redness. The PISRT decided not to proceed with evaluating the 20, 60, 120 and 200 μg bivalent rLP2086 dose levels in the infant population.

Following this decision, it was proposed that the trial be continued using dosages of 5 μg and 10 μg of the vaccine. The intention was to obtain these dosages by having the trial sites dilute the lowest vaccine formulation (20 μg). However, during the review of the Paediatric Investigation Plan by the Paediatric Committee (PDCO) of the European Medicines Agency, the comment was made that the dilution process could result in the inadvertent administration of inappropriate dose levels. This observation, combined with the conclusion by the sponsor that the safety profile of doses ≥20 μg in this age group was unacceptable due to the high rates of fever, resulted in a decision by the sponsor to terminate the study.