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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Viagra® / Sildenafil

PROTOCOL NO.: A1481283

PROTOCOL TITLE: A Follow Up Investigation for Patients Completing Study A1481276 to Investigate Developmental Progress 12 and 24 Months Following Completion of Sildenafil Treatment

Study Center: One (1) center in United Kingdom took part in the study and enrolled subjects.

Study Initiation Date and Final Completion Date: November 2012 and December 2013

Phase of Development: Phase 2

Study Objectives:

Primary Objective: To monitor the developmental progress of persistent pulmonary hypertension of the newborn (PPHN) subjects treated with sildenafil in a previous open-label study (A Single Arm Single Centre Study to Investigate Safety and Efficacy of Sildenafil in Near Term and Term Newborns With Persistent Pulmonary Hypertension of the Newborn (PPHN) [NCT01069861]), at 12 and 24 months after completion of sildenafil treatment.

Secondary Objective: To collect safety and 2-year survival data.

METHODS

Study Design: This was a single-center study to monitor the developmental progress of PPHN subjects who took part in the previous study. All subjects treated with intravenous (IV) sildenafil were eligible to participate in this follow-up study. Subjects were to return to the study site for clinical and safety follow-up and attend 2 pediatric developmental assessment appointments, 12 and 24 months (±2 months, Study Visits 1 and 2, respectively) after completion of the previous study treatment. A schedule of activities is provided in Table 1.

Table 1. Schedule of Activities

Study Activity	On Completion of Previous Study and Prior to Follow-Up Visit 1 Assessments	Follow-Up Visit 1: 12 Months (±2 Months) After End of Previous Study Treatment	Follow-Up Visit 2: 24 Months (±2 Months) After End of Previous Study Treatment
Informed consent[a]	X		
Medical history		X	X
Physical examination		X	X
Hearing test		X	X
Ophthalmology examination		X	X
Neurological examination[b]		X	X
Developmental assessments[c]		X	X
Review of ongoing medications		X----------X	
Adverse events[d]		X----------X	

a. Performed by subject's legal guardian.
b. Neurological exam based on the Hammersmith Infant Neurological Examination.
c. Based on the Bayley Scales of Infant and Toddler Development (third edition) and the Social Emotional and Adaptive-Behavior questionnaire from Bayley III.
d. Adverse events were collected at Study Visit 1 and Visit 2. Any serious adverse event occurring between end of previous study and start of current study were reported against the current study to the Sponsor's safety database.

Number of Subjects (Planned and Analyzed): There was no formal sample size planned, and only 1 subject was enrolled in the study.

Diagnosis and Main Criteria for Inclusion and Exclusion: Male or female subjects who had received sildenafil treatment in the previous study were included in the study.

Main Exclusion Criteria: Subjects who did not receive sildenafil treatment during the previous study were excluded.

Study Treatment: No study treatment was administered in this study.

Efficacy and Safety Endpoints:

Primary Endpoints:

- Physical examination, to include neurological development assessment, hearing and ophthalmology tests.
- Medical history including clinically relevant hospital admissions in the 2-year follow-up period.

Secondary Endpoints:

- Survival to 2 years.
- Adverse events (AEs).

Safety Evaluations: Safety was assessed by AE monitoring, and physical and developmental examinations.

Statistical Methods:

Full Analysis Set (FAS): The FAS was defined as all enrolled subjects.

Safety Analysis Set: The safety analysis set was the same as the FAS.

Data was to be explored through the use of standard presentations of descriptive statistics. All study assessments and AEs were summarized. Time to survival was to be summarized and displayed in Kaplan-Meier estimates and survival curves. However, since only 1 subject participated in the study and was only seen at the 12-month visit and then lost to follow-up, these were not done.

RESULTS

Subject Disposition and Demography: One (1) female subject was enrolled in the study (Table 2). The subject was seen at 12 months (Study Visit 1), and after repeated, documented, unsuccessful attempts to contact the family for Study Visit 2 (24-month follow-up visit), the subject was declared to be lost to follow-up.

Table 2. Subject Evaluation Groups

	Overall
Number (%) of subjects	
Screened	1
Completed	0
Discontinued	1 (100.0)
Ongoing at date of cut-off	0
Analyzed for safety:	
Adverse events	1 (100.0)

Demography and baseline characteristics are shown in Table 3.

Table 3. Demographic and Baseline Characteristics

	Male	Female	Total
Number (%) of subjects	0	1	1
Age (years):			
<1	0	0	0
≥1	0	1 (100.0)	1 (100.0)
Mean		1.2	1.2
Range		1.2-1.2	1.2-1.2
Race:			
White	0	1 (100.0)	1 (100.0)
Black	0	0	0
Asian	0	0	0
Other	0	0	0
Weight (kg):			
Mean		9.7	9.7
Range		9.7-9.7	9.7-9.7
N	0	1 (100.0)	1 (100.0)
Height (cm):			
Mean		75.2	75.2
Range		75.2-75.2	75.2-75.2
N	0	1 (100.0)	1 (100.0)

N = number of subjects.

Efficacy Results:

Physical Examination: The physical examination of the abdomen, lungs, mouth, nose, throat and skin performed on Visit 1 was normal (Table 4).

Table 4. Physical Examination Findings

Serial Number	Visit	Site	Evaluations	Done/Not Done
1	Follow-up 1[a] 26 November 2012	Abdomen	Normal	Done
		General	Normal	Done
		Lungs	Normal	Done
		Mouth	Normal	Done
		Nose	Normal	Done
		Other		Done
		Skin	Normal	Done
		Throat	Normal	Done
	Follow-up 2[b] 02 December 2013	Abdomen		Not done
		General		Not done
		Lungs		Not done
		Mouth		Not done
		Nose		Not done
		Other		Not done
		Skin		Not done
		Throat		Not done

a. Follow-up 1: Visit 1 conducted 12 months (±2) months following completion of treatment in previous study.
b. Follow-up 2: Visit 2 was to be conducted 24 months (±2) months following completion of treatment in previous study, but after repeated, unsuccessful attempts to contact the family for Study Visit 2, the subject was declared to be lost to follow-up.

Neurological Assessment: Neurological examination is presented in Table 5. The scores were within the normal range for the subject's age.

Table 5. Hammersmith Infant Neurological Examination

Parameters	Visit 1 26 November 2012	Visit 2 02 December 2013
	N=1	N=1
Status	Done	Not done
Gestational age (weeks)	42	-
Cranial nerve score	15/15	-
Posture score	18/18	-
Movement score	6/6	-
Tone score	24/24	-
Reflexes and reactions score	15/15	-
Neurological examination global score	78/78	-

Visit 1 conducted 12 months (±2) months following completion of treatment in previous study.
Visit 2 was to be conducted 24 months (±2) months following completion of treatment in previous study, but after repeated, unsuccessful attempts to contact the family for Study Visit 2, the subject was declared to be lost to follow-up.
N = number of subjects.

Hearing and Ophthalmology Tests: Hearing tests were not performed at the 12-month follow-up visit. At Visit 1, fundi and pupils of both eyes were examined and found to be normal for this subject; biomicroscopy of the anterior segment of both eyes was normal. Visual acuity test showed no amblyopia, strabismus or nystagmus.

Bayley III Scales of Infant and Toddler Development: The results for the Bayley Scales of Infant and Toddler Development are listed in Table 6. The scores were within the normal range for this subject's age.

Table 6. Bayley III Scales of Infant Development

Parameters	Visit 1 26 November 2012 N=1					Visit 2 02 December 2013 N=1
Area of Development	Raw Score	Scale Score	Composite Score	Percentile Rank	95% CI (%)	
Status			Done			Not done
Cognitive	46	10	100	50	92-108	-
Language						
Receptive communication	17	10				-
Expressive communication	18	10				-
Sum of language		20	100	50	93-107	-
Motor						
Fine motor	35	14				-
Gross motor	48	11				-
Sum of motor		25	115	84	106-121	-

Visit 1 conducted 12 months (±2) months following completion of treatment in previous study.
Visit 2 was to be conducted 24 months (±2) months following completion of treatment in previous study, but after repeated, unsuccessful attempts to contact the family for Study Visit 2, the subject was declared to be lost to follow-up.
CI = confidence interval; N = number of subjects.

Medical History: At the time of Study Visit 1 (12-month visit), it was reported that the subject had 2 episodes of upper respiratory tract infection in the previous year, for which no medications were required.

Survival to 2 Years: Data not available.

Safety Results:

Serious Adverse Events: Data not available.

The data from the 12-month follow-up visit did not reveal any abnormal findings in the safety assessments. The only subject enrolled in the study was seen at 12 months (Study Visit 1), and then was lost to follow-up.

Discontinuations due to Adverse Events and Deaths: Data not available.

CONCLUSION: No conclusions could be made from the assessments performed or data collected as only 1 subject was assessed at 1 study visit.