Study No.: FLR115332

Title: A Single-arm, Open Label Study Evaluating the Impact on Lifestyle of a New Thermo Stable Formulation of FLOLAN® in Subjects with Pulmonary Arterial Hypertension (PAH)

Rationale: This study in subjects with PAH was designed to describe the effect of the new thermo stable formulation of epoprostenol sodium (referred to hereafter as the reformulated product) on quality of life (QoL) in subjects switching from the currently marketed epoprostenol sodium formulation to the reformulated product, and to determine the dose titration requirement during the switch to the reformulated product.

Safe and effective administration of epoprostenol sodium by continuous intravenous infusion is complex and requires considerable commitment from subjects. The currently marketed epoprostenol sodium formulation (FLOLAN®) is provided to subjects in 2 vials: 1 containing sterile, freeze-dried powder of epoprostenol sodium equivalent to 0.5 mg or 1.5 mg of epoprostenol and another containing sterile diluent. The product requires reconstitution and dilution every 2 days and the reconstituted solution may only be administered up to 24 hours when it is maintained between a temperature of 2°C and 8°C (36°F to 46°F) during infusion, thereby, necessitating the use of a cold pack (the cold pack must be changed every 12 hours).

GSK has reformulated the diluent by increasing the target pH from 10.5 to 12.0, which makes the reconstituted product more stable (for 24 hours up to 35°C [95°F] and for 48 hours up to 25°C [77°F]), negating the use of a cold pack and frequent changes of cassette, and allowing reconstitution and dilution every 6 days. No change has been made to the vial that contains the lyophilised epoprostenol. Thus, the reformulated product is anticipated to provide an added level of convenience to patients through reduction in the frequency of reconstitution/dilution, and elimination of the need for a cold pack.

Phase: IV

Study Period: 23 November 2011 to 08-Nov-2012

Study Design: This was a multicentre, open-label, single-arm study in subjects who were receiving epoprostenol sodium (FLOLAN®) for the treatment of PAH. The study comprised 4 study periods: a Screening Visit, a 4-week Run-in Period with existing epoprostenol sodium treatment, a 4-week Treatment Period with the reformulated product and an optional Extension Phase. Following a 4-week Run-in Period, eligible subjects were admitted to the clinic for Baseline assessments and for switching to study medication (the reformulated product). Subjects remained in hospital for a minimum of 6 hours to ensure clinical and haemodynamic stability prior to discharge. Hospital admission could be extended for up to 24 to 48 hours at the discretion of the investigator. Dose titration requirement was assessed at the time of discharge. Haemodynamic parameters were obtained in a subgroup of subjects enrolled in centres where the collection of haemodynamic data was considered part of the standard of care. Subjects received study medication as a continuous intravenous infusion for 4 weeks; those who completed the 4-week Treatment Period had the option of entering the Extension Phase of the study to continue receiving the reformulated product.

Centres: Five centres in the United States, 1 centre in Canada and 1 centre in The Netherlands

Indication: PAH

Treatment: During the Run-in Period; subjects continued to take their commercial epoprostenol sodium (FLOLAN®) at the dosage previously prescribed, and prepared and administered it as previously instructed. Following the 4-week Run-in Period, subjects were administered study drug, which was prepared by reconstituting and diluting 1 or more vials of epoprostenol lyophile (according to therapeutic need) with 2 vials of sterile glycine diluent (pH 12.0), to give 100 mL of medication for each day of treatment. The switch to study drug occurred in the clinic under the supervision of study staff. Initially, the study drug was started at an equivalent dose to the subject's current commercial epoprostenol sodium treatment. If necessary, the investigator adjusted the dose, as appropriate for the subject's condition, until they were on a stable dose of the study drug. Study drug was administered by continuous infusion in the same way as the epoprostenol sodium given during the Run-in Period.

Objectives: The primary objectives of this study were to describe the effect of the new thermo stable formulation of epoprostenol sodium on QoL in subjects switching from the currently marketed epoprostenol sodium to the new thermo stable formulation and to determine the dose titration requirement in subjects switching from the currently marketed epoprostenol sodium to the new thermo stable formulation.

Primary Outcome/Efficacy Variables:

- QoL assessment using Short Form 36 (SF-36) questionnaire
- Ease of administration and changes in QoL in particular activities of daily living assessment using a study-specific questionnaire
- Change from Baseline in the dose of reformulated product at the time of discharge at a minimum of 6 hours or per local guidelines/practices.

Secondary Outcome/Efficacy Variable(s):

- 6-minute walking distance test (6MWD) after 4 weeks of treatment
- Breathlessness after 6MWD – Borg Dyspnoea Index (BDI) after 4 weeks of treatment

- World Health Organisation (WHO) functional class (FC) at Baseline and after 4 weeks of treatment

Statistical Methods: The sample size was based on feasibility. Formal hypothesis testing was not planned or performed for any of the study endpoints. The ITT population consisted of all subjects who received at least 1 dose of epoprostenol sodium (either currently marketed epoprostenol sodium during the Run-in Period or study drug during the Treatment Period and the Extension Phase). This population was used for all efficacy and safety summaries.
Primary efficacy analysis: The SF-36 questionnaire comprised 36 questions divided into 10 domains. SF-36 scores at Baseline (Visit 2) and Week 4 (Visit 3) were summarised descriptively for each domain and component score, and change from Baseline and percentage change from Baseline summaries were tabulated. No imputation was made for missing data. No formal comparison between the 2 visits was carried out. A supportive analysis was performed using last observation carried forward. Similar summaries were produced for the study-specific questionnaire, which consisted of 15 questions.
Secondary efficacy analysis: The 6MWD and the BDI were summarised descriptively by visit, and change from previous visit for Baseline (Visit 2) and Week 4 (Visit 3) were summarised. Confidence intervals (95%) were calculated for the change from Screening (Visit 1) and Baseline (Visit 2). The number and percentage of subjects with different categories of WHO FC were summarised by visit; change from last visit in WHO FC was also summarised.
Safety Analyses: Descriptive summary statistics for the daily dosage of epoprostenol sodium (both currently marketed epoprostenol sodium and study drug) were presented by visit and change from previous visit was presented for the Baseline Visit (Visit 2; first visit in the Treatment Period, following the first dose of the reformulated product) and Visit 3 (Week 4), as well as at the end of extension study visit.
Summary statistics for the difference and percent change difference between last dose during the Run-in Period and the dose at discharge during the Treatment Period were presented. Additionally, the proportion of subjects with a difference of more than 4 ng/kg/min or 6 ng/kg/min between the last Run-in dose and the last dose within the first 48 hours of switching to the reformulated product was presented separately.
All adverse events (AEs) and serious adverse events (SAEs) reported during the study were summarised. All laboratory data were presented using summary statistics, and the number and percentage of subjects with haematology and clinical chemistry values above and below the values of clinical concern were summarised. Infusion site reactions were summarised descriptively by study period; 12-lead electrocardiograms, pulse oximetry (oxygen saturation) and N-terminal pro-B-type natriuretic peptide (NT-Pro BNP) were summarised descriptively by visit. Vital signs were also summarised descriptively by visit, as well as change from Baseline at Visits 2, 3, and the end of extension visit being presented.

Study Population: Eligible subjects were men or non-pregnant, non-lactating women aged 18 to 75 years who were taking epoprostenol sodium (FLOLAN®) for the treatment of PAH, had been on a stable dose of epoprostenol sodium for at least 3 months prior to Screening, and were on stable doses of other PAH treatments for at least 30 days prior to Screening. Subjects were required to be able to walk 150 m during a 6MWD test. Subjects with a resting arterial oxygen saturation <90%, with congestive heart failure arising from severe left ventricular dysfunction, who had been hospitalised or had visited the emergency room for a PAH-related condition in the past 3 months, who were not expected to be clinically stable for the duration of the study, or who were taking epoprostenol sodium for a condition or in a manner outside the approved indication, were excluded. Additionally, subjects with a history of cancer, alcohol or illicit drug abuse, or who had active hepatitis B or C, were not eligible for the study.

Entered into the Treatment Period, N	16
Planned, N	20 (to achieve 15 completers)
Completed the 4-week Treatment Period, n (%)	16 (100)
Entered into the Extension Phase	15
Total Number Subjects Withdrawn from the Extension Phase, n (%)	15
Demographics	
N (ITT)	16
Females:Males	12:4
Mean Age, years (SD)	50.0 (13.37)
Caucasian, n (%)	15 (94)
Years since diagnosed with PAH	
n	16
Mean (SD)	6.11 (4.878)
Median	4.15
Minimum, maximum	0.5, 18.3
Diagnosis of PAH, n (%)	
Idiopathic PAH	9 (56)
Familial PAH	3 (19)

"Associated with" PAH	3 (19)
Other	1 (6)

Primary Efficacy Results:
QoL assessment using SF-36 questionnaire:

Domains	Baseline (N=16)	Week 4 (N=16)	Change from Baseline
Physical functioning			
n	16	16	16
Mean (SD)	36.224 (10.2047)	35.068 (9.1541)	-1.156 (3.6593)
Median	35.990	33.880	-1.050
Minimum, maximum	17.05, 50.72	17.05, 48.61	-6.32, 6.31
Role-physical			
n	16	16	16
Mean (SD)	40.629 (12.3529)	39.864 (10.9689)	-0.765 (6.3050)
Median	42.160	39.710	-1.220
Minimum, maximum	17.67, 56.85	17.67, 56.85	-7.35, 19.59
Role-Emotional			
n	16	16	16
Mean (SD)	46.647 (11.6081)	46.649 (9.4011)	0.002 (11.1773)
Median	50.045	44.220	0
Minimum, maximum	20.89, 55.88	32.56, 55.88	-23.32, 23.33
Vitality			
n	16	16	16
Mean (SD)	51.895 (5.7520)	52.676 (7.3193)	0.781 (7.1636)
Median	52.090	52.090	1.560
Minimum, maximum	39.60, 61.46	39.60, 64.58	-9.37, 9.37
Mental health			
n	16	16	16
Mean (SD)	52.471 (5.8957)	53.354 (6.0149)	0.883 (7.6063)
Median	52.820	55.640	0
Minimum, maximum	35.93, 61.27	41.56, 61.27	-8.45, 22.53
Social functioning			
n	16	16	16
Mean (SD)	47.988 (7.9349)	49.693 (7.1029)	1.706 (7.1043)
Median	45.940	51.400	0
Minimum, maximum	35.03, 56.85	35.03, 56.85	-10.91, 16.37
Bodily pain			
n	16	16	16
Mean (SD)	47.326 (10.0588)	50.391 (9.9386)	3.065 (5.8291)
Median	48.175	50.710	0
Minimum, maximum	29.15, 62.12	33.38, 62.12	-4.23, 18.18
General health			
n	16	16	16
Mean (SD)	41.374 (9.1249)	40.769 (10.2861)	-0.606 (5.6068)
Median	45.305	40.460	0
Minimum, maximum	25.76, 52.93	24.33, 55.32	-16.68, 8.11
Physical health component			
n	16	16	16
Mean (SD)	38.034 (9.6618)	37.911 (8.6405)	-0.123 (4.2876)
Median	39.965	39.050	-0.460
Minimum, maximum	24.85, 53.47	25.47, 50.34	-5.44, 11.99
Mental health component			
n	16	16	16
Mean (SD)	54.369 (6.2557)	55.511 (8.0542)	1.141 (6.5078)
Median	52.865	56.725	4.155
Minimum, maximum	45.52, 64.07	39.00, 67.72	-11.44, 9.36

Ease of administration and changes in QoL, in particular activities of daily living assessment using a study-specific questionnaire (Questions [Q] 1 to 15):			
Questions	**Baseline (N=16)**	**Week 4 (N=16)**	**Change from Baseline**
How much time on average in a week is required for mixing, loading and attaching your epoprostenol sodium cassette to the pump (Q1)			
n	16	16	Not applicable
Less than 1 hour	5 (31)	7 (44)	Not applicable
1 hour to 1 hour 30 minutes	5 (31)	4 (25)	Not applicable
1 hour 30 minutes to 2 hours	1 (6)	2 (13)	Not applicable
2 hours to 2 hours 30 minutes	0	1 (6)	Not applicable
Other	5 (31)	2 (13)	Not applicable
How much do you think that the pump and other items related to your epoprostenol sodium treatment interfere with the following activities (Q2 to Q5; rated from 1 [not restrictive] to 10 [extremely restrictive]):			
The ability to perform physical activities (exercising, walking, etc.) (Q2)			
n	16	16	16
Mean (SD)	4.7 (2.50)	3.8 (1.95)	-0.9 (2.29)
Median	5.0	3.5	-1.5
Minimum, maximum	1, 10	1, 8	-4, 5
The ability to perform your basic daily activities (shopping, personal care, etc.) (Q3)			
n	16	16	16
Mean (SD)	4.8 (2.35)	3.3 (1.91)	-1.5 (1.86)
Median	5.0	3.0	-1.0
Minimum, maximum	1, 8	1, 8	-5, 1
The ability to perform activities with your family (playing with your children, school activities, taking children to school, etc.) (Q4)			
n	16	16	16
Mean (SD)	4.2 (2.40)	3.4 (2.09)	-0.8 (2.37)
Median	5.0	3.0	0
Minimum, maximum	1, 9	1, 9	-6, 4
The ability to participate in social activities (leisure) (Q5)			
n	16	16	16
Mean (SD)	4.5 (2.53)	3.6 (2.19)	-0.9 (1.88)
Median	5.0	3.0	-1.0
Minimum, maximum	1, 10	1, 9	-5, 3
How comfortable are you with your ability to comply with your epoprostenol sodium treatment regimen around other activities (i.e., while travelling, working, on holidays [vacations] etc.) (Q6; rated from 1 [not comfortable] to 10 [extremely comfortable])			
n	16	16	16
Mean (SD)	7.0 (2.83)	7.3 (2.82)	0.3 (3.34)
Median	6.5	7.5	0
Minimum, maximum	1, 10	2, 10	-6, 5
If you were asked to perform a new activity such as joining a walking group, or taking up a new hobby, etc., how likely would you be to try (Q7; rated from 1 [not likely] to 10 [very likely])			
n	16	16	16
Mean (SD)	6.9 (2.36)	7.3 (2.35)	0.4 (2.00)
Median	6.5	8.0	0
Minimum, maximum	2, 10	2, 10	-5, 4
What is your overall satisfaction with your ability to perform everyday activities (Q8; rated from 1 [not satisfied] to 10 [extremely satisfied])			
n	16	16	16
Mean (SD)	6.8 (2.23)	7.3 (1.69)	0.4 (1.09)
Median	7.0	8.0	0
Minimum, maximum	3, 10	5, 10	-1, 3
Please rate how the epoprostenol sodium treatment regimen, including the pump and related items, affects your lifestyle on each of the following items (Q9 to Q12; rated from 1 [do not agree] to 10 [strongly agree]):			
I feel interested in engaging in physical activity (Q9)			

n	16	16	16
Mean (SD)	6.4 (2.68)	6.3 (2.35)	-0.1 (2.53)
Median	6.5	6.5	0
Minimum, maximum	1, 10	2, 10	-8, 3
I feel physically restricted from participating in activities due to the demands of the treatment regimen (Q10)			
n	16	16	16
Mean (SD)	4.6 (2.56)	4.7 (2.50)	0.1 (2.73)
Median	5.0	4.5	0
Minimum, maximum	1, 10	1, 10	-4, 4
I am confident in my ability to take on any new activities (Q11)			
n	16	16	16
Mean (SD)	6.4 (2.60)	6.9 (2.35)	0.6 (2.50)
Median	6.0	7.0	0
Minimum, maximum	2, 10	1, 10	-4, 5
My epoprostenol sodium treatment regimen constantly weighs on my mind (Q12)			
n	16	16	16
Mean (SD)	4.0 (2.71)	3.4 (2.66)	-0.6 (1.75)
Median	3.0	2.5	-0.5
Minimum, maximum	1, 10	1, 10	-4, 3
Within the past seven days, on how many days did you reconstitute your epoprostenol sodium solution (Q13)			
n	Not assessed	16	Not applicable
Mean (SD)	Not assessed	5.1 (2.66)	Not applicable
Median	Not assessed	7.0	Not applicable
Minimum, maximum	Not assessed	1, 7	Not applicable
In your opinion, what would be the ideal frequency to reconstitute epoprostenol sodium solution (Q14)			
n	Not assessed	16	Not applicable
Daily	Not assessed	6 (38)	Not applicable
Every second day	Not assessed	0	Not applicable
Every third day	Not assessed	3 (19)	Not applicable
Every fourth day	Not assessed	1 (6)	Not applicable
Every fifth day	Not assessed	5 (31)	Not applicable
Missing	Not assessed	1 (6)	Not applicable
Which epoprostenol sodium product do you prefer to use (Q15)			
n	Not assessed	16	Not applicable
The original (Baseline) product	Not assessed	1 (6)	Not applicable
The new product	Not assessed	14 (88)	Not applicable
I have no preference	Not assessed	1 (6)	Not applicable

Note: Questions 2 to 5, 10, and 12 are rated 1 to 10 (best to worst) and Questions 6 to 9, and 11 are rated 1 to 10 (worst to best).

Change from Baseline in the dose of reformulated product at the time of discharge at a minimum of 6 hours or per local guidelines/practices:

Change in Dosing (Treatment Period)	**Overall (N=16)**
Last dose at Run-in (ng/kg/min)	
n	16
Mean (SD)	37.73 (18.377)
Median	35.00
Minimum, maximum	14.0, 77.0
Dose at Discharge (ng/kg/min)	
n	16
Mean (SD)	37.95 (18.687)
Median	34.50
Minimum, maximum	14.0, 77.0
Difference in dose from last dose in Run-in to Discharge (ng/kg/min)	
n	16
Mean (SD)	0.22 (1.169)

Median	0
Minimum, maximum	-1.0, 4.5
Percent change difference in last dose in Run-in to Discharge (%)	
n	16
Mean (SD)	0.32 (2.335)
Median	0
Minimum, maximum	-3.3, 8.5

Extension Phase, N=15

	Daily Dosing (ng/kg/min)	**Change from Previous Visit (ng/kg/min)**
n	15	15
Mean (SD)	38.68 (19.225)	0.13 (0.516)
Median	40.00	0
Minimum, maximum	14.0, 77.0	0, 2.0

Secondary Outcome Variable(s):
6MWD after 4 weeks of treatment:

6MWD (m)	**Overall (N=14)[1]**	**Percent change from previous visit**
Screening		
n	14	Not applicable
Mean (SD)	440.42 (85.421)	Not applicable
Minimum, maximum	287.0, 578.0	Not applicable
Baseline		
n	14	Not applicable
Mean (SD)	438.59 (100.453)	Not applicable
Minimum, maximum	300.0, 651.0	Not applicable
Week 4		
n	14	Not applicable
Mean (SD)	435.05 (96.810)	Not applicable
Minimum, maximum	292.0, 687.0	Not applicable
Baseline change from Screening		
n	14	14
Mean (SD)	-1.82 (61.307)	-0.02 (13.248)
Minimum, maximum	-177.0, 92.0	-37.1, 23.0
95% CI	(-37.22, 33.58)	(-7.66, 7.63)
Week 4 change from Baseline		
n	14	14
Mean (SD)	-3.55 (45.321)	0.10 (12.403)
Minimum, maximum	-73.0, 114.0	-14.8, 38.0
95% CI	(-29.71, 22.62)	(-7.06, 7.26)

1. Two subjects (Subjects 090809/081 and 090809/082) were excluded from the 6MWD data as their assessments were not performed correctly.

Breathlessness after 6MWD – BDI:

BDI	**Overall (N=14)[1]**	**Percent change from previous visit**
Screening		
n	14	Not applicable
Mean (SD)	3.04 (2.283)	Not applicable
Minimum, maximum	0.0, 8.0	Not applicable
Baseline		
n	14	Not applicable
Mean (SD)	2.57 (2.046)	Not applicable
Minimum, maximum	0.5, 7.0	Not applicable
Week 4		
n	14	Not applicable
Mean (SD)	2.93 (2.083)	Not applicable

Minimum, maximum	0.5, 7.0	Not applicable
Baseline change from Screening		
n	14	13
Mean (SD)	-0.46 (1.117)	-4.11 (53.460)
Minimum, maximum	-2.5, 1.0	-83.3, 100.0
95% CI	(-1.11, 0.18)	(-36.42, 28.19)
Week 4 change from Baseline		
n	14	14
Mean (SD)	0.36 (0.535)	35.71 (81.350)
Minimum, maximum	0.0, 1.5	0.0, 300.0
95% CI	(0.05, 0.67)	(-11.26, 82.68)

1. Two subjects (Subjects 090809/081 and 090809/082) were excluded from the BDI data as their 6MWD assessments were not performed correctly.

WHO FC at Baseline, after 4 weeks of treatment, and at the end of the extension phase:

WHO Category	**Number (%) of Subjects (N=16)**
Screening	
n	16
WHO FC I	0
WHO FC II	10 (63)
WHO FC III	6 (38)
WHO FC IV	0
Baseline	
n	16[1]
WHO FC I	2 (13)
WHO FC II	9 (56)
WHO FC III	4 (25)
WHO FC IV	0
Week 4	
n	16
WHO FC I	2 (13)
WHO FC II	10 (63)
WHO FC III	4 (25)
WHO FC IV	0
End of Extension Study Visit	N=15
n	14[1]
WHO FC I	1 (7)
WHO FC II	7 (50)
WHO FC III	4 (29)
WHO FC IV	1 (7)

1. WHO FC data were missing for 1 subject at the visit.

Safety Results:

Most Frequent Adverse Events Occurring in 2 or more subjects in any Study Period, n (%)	Run-in Period N=16	Treatment Period N=16	Extension Phase N=15
Subjects with any AE(s)	3 (19)	9 (56)	11 (73)
Headache	1 (6)	2 (13)	0
Diarrhoea	0	2 (13)	2 (13)
Fatigue	0	2 (13)	1 (7)
Nausea	0	2 (13)	0
Oedema peripheral	0	1 (6)	3 (20)
Device-related infection	2 (13)	0	3 (20)
Anaemia	0	0	2 (13)
Hypotension	0	0	2 (13)
Thrombosis in device	0	0	2 (13)

1. Sorted by frequency in the Treatment Period.

Serious Adverse Events - On-Treatment[1], n (%)
n (%) [n considered by the investigator to be related to study medication]

	Run-in Period N=16	Treatment Period N=16	Extension Phase N=15
Subjects with non-fatal SAEs, n (%)	2 (13)	1 (6)	3 (20)
	n (%) [related]	**n (%) [related]**	**n (%) [related]**
Catheter site haemorrhage	0	1 (6) [0]	0
Device-related infection	2 (13) [0]	0	0
Thrombosis in device	0	0	1 (7) [0]
International normalised ratio increased	0	0	1 (7) [0]
Pulmonary arterial hypertension	0	0	1 (7) [0]
Subjects with fatal SAEs, n (%)	0	0	0

1. Sorted by frequency in the Treatment Period.

Conclusion:

There were small changes in the mean scores for some of the SF-36 domains after transition from the currently marketed epoprostenol sodium to the reformulated product, with small positive changes in 6 of the 10 domains and small negative changes in 4 domains. For the rated study-specific questionnaire items (Questions 2 to 12), there were small improvements in the mean scores for 9 of the 11 items with the reformulated product compared with the currently marketed epoprostenol sodium, and 14 of the 16 subjects (88%) stated a preference for the reformulated product. The difference in dose from the last dose in the Run-in Period to the time of discharge was 0.22 ng/kg/min. No new safety signals were identified during the study. The observed safety profile for the reformulated product was consistent with the current labeling for FLOLAN®.