2 SYNOPSIS

NAME OF SPONSOR/COMPANY: Vantia Ltd.		
NAME OF FINISHED PRODUCT: VA111913 TS Capsules		
NAME OF ACTIVE INGREDIENT: VA111913 TS		
Title of Study: A Randomised, Double-Blind, Placebo-Controlled, Multicentre, Cross-Over Proof of Concept Study to Investigate the Efficacy and Safety of Pre-Emptive Administration of Repeated, Oral Doses of VA111913 TS for the Alleviation of Dysmenorrhoea		
Primary Site Investigators (Active Study Centres): [redacted]		
Publication (ref.): None		
Study Period: **(date of first enrolment):** 16th September 2009 **(date of last completed):** 22nd September 2010	**Phase of Development:** II	

Primary Objective: To investigate the efficacy of pre-emptive (prior to the onset of menstrual pain and bleeding), repeated, orally administered VA111913 TS compared to Placebo on the reduction of menstrual pain in women with primary dysmenorrhoea.

Secondary Objectives:

- To investigate the effects of pre-emptive VA111913 TS on the need for rescue medication usage for dysmenorrhoea
- To establish the safety profile of pre-emptive administration of VA111913 TS
- To investigate the effect of VA111913 TS on menstrual bleeding patterns
- To preliminarily explore the pharmacokinetic (PK)/pharmacodynamic (PD) relationship of pre-emptive VA111913 TS
- To explore the correlation between trough plasma VA111913 concentration and time-weighted sum of pain intensity (SPI) scores on an 11-point Numerical Rating Scale (NRS) assessed as the SPI scores for the 24 hours after the onset of bleeding
- To explore the correlation between trough plasma VA111913 concentration and the worst pain intensity in the treatment cycle
- To explore the correlation between the luteinising hormone (LH) surge and the subject's prediction of the onset date of menstruation based on menstrual history and occurrence of usual premenstrual prodromal symptoms to facilitate the determination of treatment onset date in future clinical studies without the need for LH monitoring

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Methodology: This was a Phase II, randomised, double-blind, Placebo-controlled, repeated dose study of the efficacy and safety of pre-emptive VA111913 TS versus Placebo for the reduction of menstrual pain in women with a consistent history of primary dysmenorrhoea.

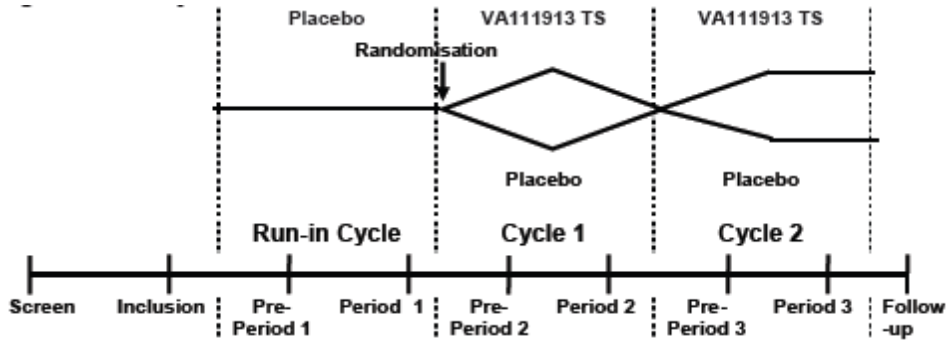
Subject participation was for 3 treatment cycles. The first treatment cycle was a single-blind Run-in Cycle during which subjects were administered Placebo, followed by 2 treatment cycles during which the subject received VA111913 TS or Placebo in a double-blind cross-over design as shown in Figure S1. During each of the 3 cycles, each subject was provided with a subject electronic diary (eDiary) to capture LH surge results, presence of usual premenstrual prodromal symptoms, start time of menses onset, menstrual pain intensity, study and rescue medications, bleeding intensity and overall subject evaluations of study treatment. Subjects could maintain normal daily activities throughout the study duration.

Frequency and/or severity of symptoms commonly associated with dysmenorrhoea were further assessed using a validated questionnaire (the Moos Menstrual Distress Questionnaire [MDQ]) at the end of menstrual flow for each menstrual cycle.

Adverse events (AEs) and concomitant medications were recorded on take-home worksheets throughout the treatment cycles.

During the 3 cycles, blood samples were taken for PK assessments of VA111913 and standard safety assessments were performed.

Figure S1 Study Outline



VA111913 TS/Placebo administration in each treatment cycle began 2 days prior to the anticipated onset of bleeding. Treatment onset was predicted according to the time of ovulation based on the subject detecting LH surge. Once an LH surge was detected, subjects informed the clinic immediately and initiation of dosing in the clinic was scheduled. The subject recorded the actual date/time of onset of menses, defined as the first observed menstrual bleeding, by pushing the “onset of menses” button on the eDiary (Time Zero for menses). If menstrual bleeding started during sleep, the subject was to push the “onset of menses” button after first noticing the start of bleeding when awake.

The Run-in Cycle consisted of a suitability assessment, confirmation of usual premenstrual prodromal symptoms and enabled the subjects to gain experience with the study tools, procedures, assessment time table and outcome measures as well as to gauge treatment compliance. At the end of the Run-in Cycle, subjects were reviewed for eligibility for

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randomisation. Only subjects recording a pain intensity score ≥ 4 on an 11-point NRS (at least 1 time point between Day -2 and Day 3 [Day 0 was the day of expected onset of menstruation based upon LH surge]) were considered eligible for randomisation.

Subjects received a single-blind treatment course of Placebo during the Run-in Cycle and were randomly assigned to a double-blind treatment course of VA111913 TS or Placebo in a cross-over design for the 2 subsequent treatment cycles. Each treatment course lasted a minimum of 5 days and a maximum of 6 days. Dosing began 2 days prior to the expected onset of menstruation (Day -2) and continued until Day 2 or Day 3. If a subject started to bleed on Day 2 or up to 8 AM on Day 3 then the subject was asked, via the eDiary, to continue to take treatment for an additional day (i.e., during Day 3) for a total of 6 days. Subjects were asked to attend the clinic prior to dosing on Day -2 for a urine pregnancy test and confirmation of continued eligibility. Any subjects who had already started bleeding or were experiencing menstrual pain had a "holiday cycle" and were not treated with study medication during that cycle. During a holiday cycle subjects were allowed to take their normal treatment for dysmenorrhoea, which was recorded as a concomitant medication. A total of 3 holiday cycles were permitted.

The first dose of study medication for each cycle (Time 0_D) was administered in the clinic. Prior to dosing and at approximately 2 hours after Time 0_D (2 hours being the estimated time of maximum plasma concentration [estimated C_{max}]), blood pressure and pulse were recorded, a 12-lead electrocardiogram (ECG) was performed and a blood sample taken for PK analysis. The ECG tracings were reviewed by the investigator on Day -2 preferably before the next dose of study medication. The subject was discharged from the clinic with the remainder of the study medication course and standard rescue medications (1st line: acetaminophen/paracetamol tablets; and 2nd line: naproxen; both administered according to labelling).

If the subject had not started bleeding by the Day 3 visit, a urine pregnancy test was performed. Subjects with a negative result entered a holiday cycle. If they still did not start bleeding after this visit, then they returned to the study centre for an unscheduled study visit within 5 days after the Day 3 visit and another urine pregnancy test was performed. Subjects in a holiday cycle were to begin LH surge testing 9 days from the bleeding onset of their previous cycle.

All subjects who took at least 1 dose of study medication for a treatment course attended a Cycle Completion Visit at the end of that treatment cycle. At this visit a blood sample was taken to determine trough concentrations of VA111913 and assessments of blood pressure, pulse and clinical laboratory safety performed together with review of the eDiary, AE and other medication worksheets. Subjects were also required to attend a final Follow-up Visit 10 days after the last intake of study medication (Day 13 ± 2 of the final cycle).

Number of Subjects (planned and analysed):

Planned: Approximately 128 subjects enrolled to obtain 102 subjects who completed both the VA111913 TS and Placebo treatment arms of the 2 × 2 cross-over study

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Analysed: 146 subjects (enrolled); 145 subjects dosed (Safety population); 103 subjects (intent-to-treat population [ITT]); 81 subjects (modified-intent-to-treat population [MITT]); 63 subjects (per-protocol population [PP]); population for responder analysis: 76 subjects (MITT2).

Diagnosis and Main Criteria for Inclusion: Healthy women aged 18 – 35 years with:

- regular menstrual cycles (typically between 25 and 35 days and of a fixed length ± 2 days every month);
- not pregnant, planning pregnancy or lactating;
- no use of hormonal contraceptives within 6 months;
- a consistent history of primary dysmenorrhoea with onset within 4 years of menarche;
- no known secondary dysmenorrhoea;
- symptoms severe enough to require medication for relief;
- impairment of daily activity if not treated.

Test Product, Dose and Mode of Administration, Batch Number:

A total of ten doses of VA111913 TS 100 mg (batch number: BMR/09/686) were administered orally twice daily at approximately 8 AM and 8 PM for 5 days during either Treatment Cycle 1 or Treatment Cycle 2. A further 2 doses were given on a 6th day depending on menstrual bleeding onset.

Duration of Treatment:

VA111913 TS was administered for a minimum of 5 days and a maximum of 6 days.

Reference Therapy, Dose and Mode of Administration, Batch Number:

A total of ten doses of Placebo (batch number BMR/09/685) was administered orally twice daily at approximately 8 AM and 8 PM for 5 days during the Run-in Cycle. A further 2 doses were given on a 6th day depending on menstrual bleeding onset.

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CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy endpoint was the time-weighted SPI scores on an 11-point NRS assessed as the SPI scores for the 24 hours after the onset of bleeding (SPI-24a).

Secondary efficacy endpoints included the following:

- Time-weighted SPI scores on an 11-point NRS assessed as the SPI scores for the 24 hours prior to the onset of bleeding (SPI-24b)
- Pain intensity scores throughout the assessment period.
- Worst pain reported.
- Duration of pain
- Subject's global evaluation of the study medication's effectiveness assessed at the end of each treatment cycle.
- Subject's comparison to the usual method of treatment for dysmenorrhoea assessed at

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the end of each treatment cycle.

- Subject's assessment of bleeding intensity assessed every evening during each treatment cycle from the start of bleeding to the time of bleeding cessation. Highest bleeding intensity experienced for each treatment cycle was also evaluated.
- Duration of bleeding
- Requirement for rescue medication use by treatment cycle (incidence of rescue medication use [1st line, 2nd line, any] and, number of rescue doses [1st line, 2nd line, any, using categories 0 to 4 and > 4]).
- Subscale scores using the Moos MDQ.

The exploratory efficacy endpoints included the deviation in subject's predicted date of bleeding start, based on menstrual history and occurrence of usual premenstrual prodromal symptoms, compared with actual date of menses onset.

Pharmacokinetics: PK evaluations included the VA111913 plasma concentrations (pre-dose and at estimated time of C_{max} and trough). The PK/PD relationship included correlation analyses between SPI-24a and SPI-24b with VA111913 plasma concentration at treatment cycle completion (at estimated time of trough),

Safety: Safety was evaluated by the incidence of treatment-emergent AEs (observed and reported) and by changes in clinical laboratory test results, vital signs and ECG and physical examination findings.

STATISTICAL METHODS:

Analysis Populations

- **ITT**: All randomised subjects who received at least 1 dose of randomised study medication.
- **MITT**: All randomised subjects who had no bleeding and no pain[1] prior to first dose of study medication, and who received at least 1 dose of study medication in the 12 hour time interval immediately prior to the onset of menses and at least 1 dose of study medication in the 24-hour time interval following the onset of menses, in each of the randomised treatment cycles and who had at least 1 postdose efficacy (i.e., pain) assessment present from each of the randomised treatment cycles. Hence any subject who did not have bleeding onset (i.e., not started bleeding by 8 am on Day 3) during either of the randomised treatment cycles was excluded from the MITT population.
- **PP**: All subjects in the MITT population who did not have any major protocol deviations in either randomised treatment cycle.

[1] Note: Subject was determined to be eligible for dosing by the centre staff prior to dosing by answering "No" to the questions "Is the subject currently bleeding?" and "Is the subject currently experiencing menstrual pain?". If both questions were answered "No", the subject could be in the MITT population. Subjects were not required to have recorded an NRS of 0 pre-dose to be in the MITT population. In cases where subjects had recorded an NRS > 0, the centre staff verified that the subject was not in pain before dosing (a data clarification form had been raised and a site comment

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- **Safety**: All subjects who received any study medication at any time (Run-in and randomised treatment cycles) during the study.
- **MITT2**: All MITT population subjects who also met the MITT requirements during the single-blind Run-in Cycle.

Disposition and Subject Characteristics

Subject disposition, demographic and baseline characteristics (including menstrual and dysmenorrhoea history) and incidence and reasons for holiday cycles as well as medication concomitant with study medication, study medication administration and compliance were tabulated by treatment sequence and both treatment sequence groups combined.

Efficacy Analyses

The primary efficacy null hypothesis was that there was no difference between VA111913 TS and Placebo with respect to SPI-24a. Time-weighted SPI was calculated as the sum of each time interval duration (between successive pain assessments) multiplied by pain intensity at the end of that interval. Pain intensity scores were imputed using last observation carried forward (LOCF) and worst observation carried forward (WOCF) approaches for missing pain assessments and after rescue or analgesic medication. SPI-24a was analysed with an analysis of variance (ANOVA) model appropriate for a cross-over design, including terms for treatment sequence, centre, subject within sequence and centre, treatment period and interaction between treatment sequence and centre. Testing was 2-sided with alpha = 0.05. The primary efficacy analysis was based on the MITT population with the PP population being supportive.

SPI-24b and worst pain recorded were analysed as for SPI-24a and these were presented descriptively. Mean pain intensity scores (in intervals: prior to bleeding onset; from bleeding onset up to but not including 24 hours post onset; for the remainder of scheduled pain assessments; and prior to rescue or analgesia medication), bleeding intensity and subscale scores of the Moos MDQ were presented descriptively for the MITT population.

Duration of pain (time between first and last non-zero pain score [on or before last scheduled pain assessment at 8 PM on Day 5 or 6], censored if pain present at last assessment) and bleeding (time between first and last reported bleeding, censored if reported bleeding at last recorded assessment) were summarised using Kaplan-Meier percentiles and analysed using a Cox Proportional Hazards Regression model for each treatment cycle for the MITT population.

Subject's global evaluation of the study medication's effectiveness, subject's comparison to the usual treatment method, subject's highest bleeding intensity and the number of rescue medication administrations (1st line, 2nd line, any) were analysed for the MITT population using the generalised McNemar's (Stuart-Maxwell) test.

Pharmacokinetic Analyses

VA111913 plasma concentrations were summarised descriptively for the MITT population (by VA111913 TS cycle and both VA111913 TS cycles combined) and correlations between

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estimated trough plasma concentration and SPI-24a and SPI-24b were evaluated using regression techniques.

Safety Analyses

All safety data were summarised descriptively for the Safety population for Run-in, treatment within treatment sequence and both treatment sequence groups combined. Summaries included incidence of TEAEs (overall, by relationship to Investigational Medicinal Product (IMP) and by severity). Listings were produced for AEs leading to withdrawal, serious adverse events (SAEs) and deaths.

For ECG intervals, vital signs endpoints and clinical laboratory test results, actual values and change from pre-dose were summarised and shifts in laboratory parameters were tabulated descriptively. Physical examination findings were listed.

Responder Analysis

An exploratory responder analysis was conducted in order to identify a potential "Target population" for VA111913 TS who may represent a subpopulation in whom vasopressin mechanism is a predominant factor in dysmenorrhoea pain. A responder was identified as any MITT2 population subject whose primary endpoint, SPI-24a score was lower in the VA111913 TS treatment cycle (either Treatment Cycle 1 or 2, depending on treatment sequence group allocation) compared to that in the Run-in Cycle (i.e. baseline).

Statistical analyses were conducted on this Target population to evaluate the effect of VA111913 TS in comparison to randomised Placebo, on the primary endpoint (SPI-24a) and secondary endpoints (worst pain; duration of bleeding; global evaluation of study medication's effectiveness; number of rescue medication administrations). Methods used were as described above, for the pre-specified analyses. The latter 2 parameters were also evaluated considering only those subjects expressing a 'preference' in a test of overall bias.

To explore the relevance of the responder analysis in the Target population, a Placebo Responder population was also examined using the same method of identification. Hence, a Placebo Responder was identified as any MITT2 population subject whose primary endpoint, SPI-24a score was lower in the Placebo treatment cycle (either Treatment Cycle 1 or 2, depending on treatment sequence group allocation) compared to that in the Run-in Cycle (i.e. baseline). Statistical analysis was conducted on the Placebo Responder population for the SPI-24a parameter and supporting secondary endpoint parameters, as described above.

RESULTS:

Subject Characteristics: The baseline demographics of the ITT population are summarised in Table S1. Overall the treatment sequence groups were similar with respect to all demographic and baseline characteristics.

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Table S1 Demographics: ITT

	VA111913 TS/ Placebo (N=52)	Placebo / VA111913 TS (N=51)	ITT Population (N=103)
Age: Mean (SD)	25.1 (4.8)	24.8 (4.8)	25.0 (4.8)
Median	24	25	25
Ethnicity: Hispanic	10%	10%	10%
Race:			
White/Caucasian	50 (96%)	48 (94%)	98 (95%)
African American	0	2 (4%)	2 (2%)
Asian	2 (4%)	1 (2%)	3 (3%)
BMI: Mean (SD)	23.6 (3.6)	23.6 (2.7)	23.6 (3.2)
Median	22.9	23.1	23.1

Efficacy Results: There was a small reduction in SPI-24a during treatment with VA111913 TS compared to Placebo which was not statistically significant in both the MITT and PP populations (Table S2), although the reduction was greater in the PP population. In the MITT population, the statistical hypothesis of equal treatment means was not rejected at the 5% level of significance. The treatment effect (VA111913 TS – Placebo) was estimated at -9.03, 95% confidence interval [CI] -26.94 to 8.88, p=0.319). Hence superiority of VA111913 TS over Placebo was not demonstrated in the total primary analysis population.

There was a statistically significant reduction in worst pain and greater percentage of subjects with a better global evaluation of treatment effectiveness on VA111913 TS compared with Placebo. The PK:PD relationship (trough concentration [VA111913]: SPI-24a) showed a statistically significant correlation (Table S3).

Non-statistically significant trends towards efficacy of VA111913 TS was seen in the endpoints of number of rescue medication administrations and comparison to subject's usual treatment. Summary statistics for mean pain (0 to <24 hours after bleeding onset) and mean pain (24 hours or more after bleeding onset) also showed reductions in pain with VA111913 TS compared with Placebo treatment.

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The treatments were similar with respect to pre-menstrual pain (assessed both as SPI-24b and mean pre menstrual pain), mean pain at time of rescue medication, highest bleeding intensity, duration of pain and bleeding and Moos MDQ subscale scores.

Table S2 Primary Efficacy Endpoint Results: MITT and PP

Primary Endpoint	MITT Population		PP Population	
	VA111913 TS	Placebo	VA111913 TS	Placebo
	N=81		N=63	
Time-weighted SPI Score for the 24 hours After the Onset of Bleeding (SPI-24a)				
Adjusted mean	106.57	115.60	110.85	124.18
Difference (95% CI) p-value[a]	-9.03 (-26.94, 8.88) p=0.319		-13.33 (-34.75, 8.09) p=0.218	

ANOVA = analysis of variance; CI = Confidence interval; MITT = modified-intent-to-treat; N = Number of subjects; SPI = sum of pain intensity.

[a] From ANOVA model with terms for treatment sequence, subject within sequence and centre, centre, treatment, period and interaction between treatment sequence and centre: Difference (VA111913 TS - Placebo).

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Table S3 Secondary Efficacy Endpoint Results: MITT

Secondary Endpoint	**VA111913 TS**	**Placebo**
	N=81	
Worst pain intensity reported		
Adjusted mean	5.87	6.63
Difference (95% CI)	-0.76 (-1.33, -0.18)	
p-value[a]	p=0.011	
Subject's global evaluation of study medication's effectiveness		
Better effectiveness n (%)	38/80 (47.5%)	19/80 (23.8%)
p-value[b]	p=0.012	
Correlation: SPI-24a and plasma concentration at estimated time of VA111913 trough		
Regression slope estimate (95% CI)	-0.2391 (-0.4634, -0.0149)	
p-value[c]	p=0.037	

ANOVA = analysis of variance; CI = Confidence interval; MITT = modified-intent-to-treat; N = Number of subjects; SPI = sum of pain intensity.

[a] From ANOVA model with terms for treatment sequence, subject within sequence and centre, centre, treatment, period and interaction between treatment sequence and centre: Difference (VA111913 TS - Placebo).

[b] From Overall Bias test, Bishop, Fienberg, Holland.

[c] From regression analysis with SPI-24a as outcome variable and VA11913 plasma concentration at estimated time of trough, as independent variable.

Exploratory Responder Analysis:

Evaluation of the distributions of SPI-24a values for each treatment by cycle combination indicated a clearly skewed distribution for SPI-24a during VA111913 TS treatment. The observed departure from normality suggests the presence of separate populations, e.g., a sub-population who responds and a sub-population who does not.

This hypothesis is supported by a *post hoc* responder analysis in subjects who had any

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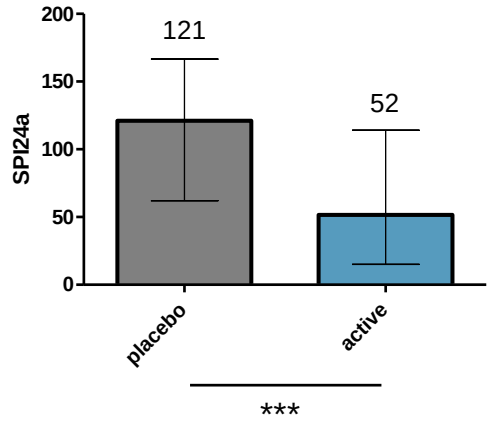
response to treatment with VA111913 TS relative to response during the Placebo Run-in Cycle (i.e. Target population). In this population, of 46 subjects (approximately 60% of the MITT2 population), there was a statistically significant reduction in SPI-24a during randomised VA111913 TS compared with Placebo treatment ($p<0.001$, estimate of treatment effect 45.1, 95% CI 23.9 to 66.2), see Figure S2.

Statistically significant treatment effects were also shown between randomised Placebo and VA111913 TS for the endpoints: worst pain; number of rescue medication administrations and global evaluation of treatment effectiveness as illustrated in Figure S3 to S5 below.

Figure S2 SPI-24a Results for the Target Population

Data are presented for both treatment sequence groups combined, as medians (also shown in text above columns) and interquartile ranges. ***P<0.001 (ANOVA)



ANOVA = analysis of variance

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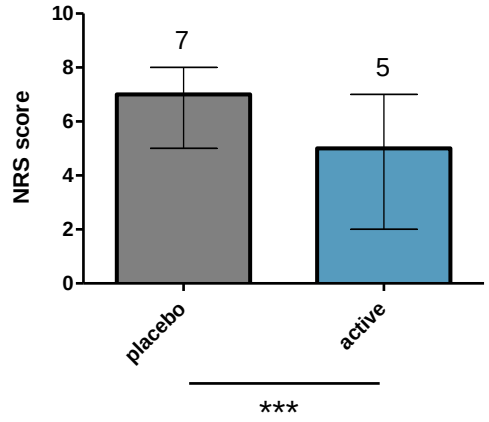
Figure S3 Worst Pain Results for the Target Population

Data are presented for both treatment sequence groups combined, as medians (also shown in text above columns) and interquartile ranges. ***P<0.001 (ANOVA)



ANOVA = analysis of variance; NRS = numerical rating scale

Figure S4 Global Evaluation Of Treatment Effectiveness Results for the Target Population

Represents the percentage of subjects who expressed a preference for either Placebo or Active treatment during the randomised treatment periods. ***P<0.001 (overall bias test)

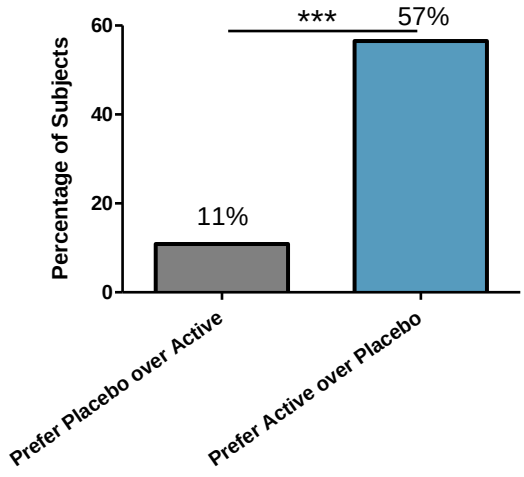


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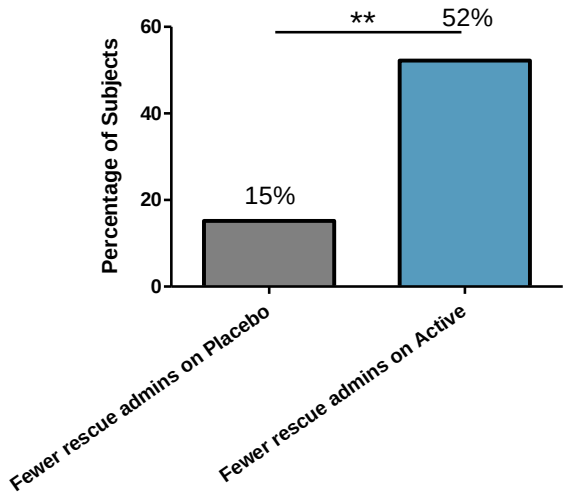
Figure S5 Rescue Medication Results for the Target Population

Represents the percentage of subjects who expressed a preference for either Placebo or Active treatment during the randomised treatment periods, with respect to number of rescue medication administrations **P<0.01 (overall bias test)



Notably, an analysis of SPI-24a and supporting secondary endpoints in Placebo Responders did not result in a statistically significant treatment effect between randomised VA111913 TS and Placebo.

Safety Results: The reported incidence rate of TEAEs in randomised subjects was 35/103 (34%) during the single-blind Placebo Run-in period. During the randomised treatment period, incidence rates of TEAEs following VA111913 TS were 20/98 (20%) and 22/96 (23%) following Placebo. IMP-related (defined as at least possibly related to study treatment or not assessable) AEs post randomisation were 2/98 (2%) and 4/96 (4%) (VA111913 TS; Placebo respectively). No serious adverse events were reported during the course of the study and no subject was withdrawn from the study as a result of an adverse event following randomised treatment. In randomised subjects, severe TEAEs were reported in 8/103 (8%) [single-blind Placebo Run-in]; 5/98 (5%) [randomised VA111913 TS]; and 7/96 (7%) [randomised Placebo]; TEAEs with a maximum severity of moderate were reported in 16/103 (16%) [single-blind Placebo run-in]; 7/98 (7%) [randomised VA111913 TS]; and 8/96 (8%) [randomised Placebo].

The most frequently reported TEAEs (regardless of relationship assessment) following randomised treatment are summarised in Table S4.

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Table S4 Incidence of TEAEs (with >1 Report Following Either Randomised Treatment) by Preferred Term for Randomised Treatment Cycles, Safety Population

Adverse Event (Preferred Term)	**VA111913 TS (N=98)**	**Placebo (N=96)**
Headache	4 (4%)	4 (4%)
Vomiting	2 (2%)	2 (2%)
Oropharyngeal Pain	2 (2%)	1 (1%)
Contusion	2 (2%)	0
Ear Pain	2 (2%)	0
Upper Respiratory Tract Infection	2 (2%)	0
Cough	1 (1%)	2 (2%)
Pyrexia	1 (1%)	2 (2%)
Nasal Congestion	0	3 (3%)
Hyperkalaemia	0	3 (3%)
Fatigue	0	2 (2%)
Pain	0	2 (2%)

TEAE = treatment emergent adverse event; N = Number of subjects receiving treatment during randomised treatment cycles (both treatment sequence groups combined)

There were no significant shifts in vital signs, laboratory or ECG parameters observed on study treatment.

CONCLUSION:

Treatment with VA111913 TS was generally very well tolerated. No serious adverse events were reported during the course of the study and no subject was withdrawn from the study as a result of an adverse event following randomised treatment. Reporting rates of TEAEs following randomised VA111913 TS or Placebo were similar in terms of nature, frequency,

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severity and relationship to IMP.

In the MITT and PP populations, reduction in SPI-24a during VA111913 TS compared with Placebo treatment was not statistically significant. However, the larger treatment effect seen in the PP population in addition to the statistically significant treatment effects observed in some of the secondary endpoints (reduction in worst pain, improved global evaluation of treatment effectiveness and PK:PD correlation) as well as trends towards a positive effect of VA111913 TS compared to Placebo treatment in other relevant endpoints (number of rescue medication administrations and comparison to usual treatment in subjects with unequal values), may be indicative of potentially beneficial pharmacological activity of VA111913 TS.

Given the heterogeneity within the population presenting with primary dysmenorrhoea in this study (in whom secondary dysmenorrhoea could not have been conclusively excluded), it can be hypothesised that vasopressin-related dysfunctional uterine contraction and ischaemia may not have been the dominant factor in the aetiology of dysmenorrhoeic pain in all women. The *post hoc* responder analysis identified a potential target population for treatment with VA111913 TS which represented approximately 60% of the MITT2 population eligible for consideration in the analysis. A clinically and statistically significant inhibition of pain during VA111913 TS treatment compared with during Placebo treatment, approaching a 60% reduction in median SPI-24a, was demonstrated in this target population. These findings were supported by statistically significant reductions in worst pain, reduced number of rescue medication administrations and improved global evaluation of effectiveness with VA111913 TS treatment in this population. This population may be identified *a priori* in future studies by way of an enrichment study design.