

A first-in-human study of PDC3 I (prostaglandin F_{2α} receptor inhibitor) in primary dysmenorrhea

B. Böttcher^{1,†}, R.M. Laterza^{2,†}, L. Wildt¹, R.J. Seufert², K.J. Buhling³, C.F. Singer⁴, W. Hill⁵, P. Griffin⁵, B. Jilma⁶, M. Schulz⁷, and R.P. Smith^{8,*}

¹Department of Gynecological Endocrinology and Reproductive Medicine, Innsbruck Medical University, Innsbruck 6020, Austria ²Department of Obstetrics and Gynecology, University of Mainz, Mainz 55131, Germany ³Department of Gynecological Endocrinology, Clinic of Gynecology, University Hospital Hamburg-Eppendorf, Hamburg 20246, Germany ⁴Department of Obstetrics and Gynecology, Medical University of Vienna, Vienna 1090, Austria ⁵PDC Biotech GmbH, Vienna 1010, Austria ⁶Department of Clinical Pharmacology, Medical University Vienna, Vienna 1090, Austria ⁷SciAn Services Limited, Toronto, Canada M8X 1X3 ⁸Division of General Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis, IN 46202, USA

*Correspondence address. Tel: +1-317-880-3959; E-mail: rogpsmit@iupui.edu

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STUDY QUESTION: What is the safe and pharmacodynamically active dose range for PDC3 I (prostaglandin F_{2α} receptor inhibitor) in patients with primary dysmenorrhea (PD)?

SUMMARY ANSWER: The 1 mg/kg/h dose of PDC3 I appears to be safe and potentially effective in reducing intrauterine pressure (IUP) and pain associated with excessive uterine contractility when given as a 3-h infusion in patients with PD.

WHAT IS KNOWN ALREADY: PDC3 I has previously been shown to reduce the duration and strength of PGF_{2α}-induced contractions in human uterine myometrial strip models and to delay delivery in animal models of preterm labor.

STUDY DESIGN, SIZE, DURATION: This was a prospective, multi-center, dose-escalating first-in-human Phase I study conducted from March 2011 to June 2012. A total of 24 women with PD were enrolled and treated with one of five doses (0.01, 0.05, 0.15, 0.3, 0.5 and 1 mg/kg/h) of PDC3 I given as a 3-h infusion. Patients were observed for a further 24 h.

PARTICIPANTS/MATERIALS, SETTING, METHODS: This study was conducted at four hospitals in Europe in non-pregnant, menstruating women with PD. Women with PD ($n = 24$) received PDC3 I infused over 3 h within 8–10 h of the onset of menstruation. IUP and pain monitoring through the visual analog scale (VAS) was assessed prior to, during and following the infusion. Patients were observed for dose-limiting toxicities and other adverse events. Pharmacokinetic samples were also taken to profile the drug.

MAIN RESULTS AND THE ROLE OF CHANCE: A 3-h infusion of PDC3 I was safe up to and including doses of 1 mg/kg/h. Most adverse events were mild ($n = 15$; 83.3%) and not considered associated with PDC3 I ($n = 14$; 77.8%). PDC3 I infusion decreased uterine activity based on IUP and pain (VAS) scores. IUP was decreased by 23% over all dose levels, reaching a minimum at 135–150 min. There appeared to be a dose-dependent effect on IUP, with the high dose group (1 mg/kg/h) showing the largest decrease in IUP. There was a statistically significant linear dose–effect and concentration–effect relationship for several IUP parameters over the evaluation period of 60–180 min. A dose differentiating effect on pain was seen with the two highest doses. PDC3 I demonstrated uncomplicated, linear pharmacokinetics with a terminal half-life of ~2 h.

LIMITATIONS, REASONS FOR CAUTION: This was a first-in-human study and exposure to PDC3 I was limited for safety reasons. As such, pharmacodynamic parameters were assessed at a two-sided Type I error of 20%, an appropriate level for the exploratory nature of this study without a placebo control arm. This limited the chance of false positive findings to one in five.

WIDER IMPLICATIONS OF THE FINDINGS: Like PD, preterm labor is associated with prostaglandin-mediated uterine contractions; therefore, the findings of this study support further development of PDC3 I as a treatment for both PD and preterm labor.

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[†] The authors consider that the first two authors should be regarded as joint First Authors.

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Introduction

The prostaglandin F_{2α} (PGF_{2α}) receptor inhibitor, PDC31, is a therapeutic peptide being developed for the treatment of preterm labor and primary dysmenorrhea (PD). The amino acid sequence is based on a transmembrane domain of the human PGF_{2α} receptor. PDC31 is an allosteric modulator of this receptor and exerts its effects at a site distinct from the binding site of PGF_{2α} (Goupil et al, 2010). It is thought to interfere with certain interactions between specific PGF_{2α} receptor domains, thereby increasing PGF_{2α}-mediated signaling via the G_{αq}-PKC-MAPK pathway, while decreasing signaling through the G_{α12}-Rho-ROCK pathway resulting in inhibition of smooth muscle contraction (Goupil et al, 2010). PDC31 has been shown to reduce the duration and strength of PGF_{2α}-induced contractions in myometrial strip models and to delay delivery in animal models of preterm labor (unpublished data; Friel et al, 2005; Hirst et al, 2005).

This first-in-human study was conducted in non-pregnant, menstruating women with PD because this was considered a much safer group of patients in which to perform a dose-finding study than the target population of pregnant women with preterm labor. Like preterm labor, PD is associated with prostaglandin-mediated uterine contractions. During menstruation, arachidonic acid released from endometrial sloughing is converted to PGF_{2α}, prostaglandin E₂ and leukotrienes (Sales and Jabbour, 2003). Prostaglandins induce uterine smooth muscle contractions which manifest as labor-like lower abdominal and back pain (Roth-Brandel et al, 1970). Prostaglandin-mediated contractions can last several minutes and produce uterine pressures of >400 mmHg, five times greater than pressures found during labor and 20 times greater than those found in women without dysmenorrhea (Smith, 1987).

The aim of this study was to determine a safe and effective dose range for PDC31, specifically looking at toxicities and reductions in intrauterine contractility and pain.

Materials and Methods

Study design

This was a prospective, multi-center, dose-escalating, first-in-human trial of PDC31 in women with PD to determine the maximum tolerated dose (MTD) of PDC31. Dose-escalation and dose-finding were governed by the modified continual reassessment method (mCRM) which calls for treating patients at the current best estimate of MTD (Schulz and Chung-Hun, 1994). MTD was defined as the dose level that is estimated to produce dose-limiting toxicities in 33% of the patients. The dose of PDC31 was escalated based on the recommendation of the Steering Committee for this study. Voting membership of the Steering Committee was comprised of a representative of the sponsor company, a biostatistician, a non-investigator gynecologist and a clinical pharmacologist. The Steering Committee met after the completion of each dose cohort and after evaluation of the safety and pharmacodynamic outcomes. The Steering Committee also recommended the number of patients to be enrolled in the next cohort. Dose escalation was to continue until the MTD was found or until a maximum of 24 patients

had been treated in this study. The doses of PDC31 tested in this study included 0.01, 0.05, 0.15, 0.3, 0.5 and 1 mg/kg/h. The starting dose was 0.05 mg/kg/h.

This dose range for PDC31 was considered safe based on the repeat dose toxicology studies conducted in both rats and dogs (unpublished data). This range was also selected to include doses which were considered potentially effective for treatment of preterm labor, based on the extrapolation of *in vivo* efficacy observed in both mouse and sheep models of preterm labor (unpublished data; Hirst et al, 2005). The range included lower doses that were considered to be below the effective range, but would provide a greater safety margin. Although the mCRM design does not incorporate a control group, the premise was that the lower doses (0.01 and 0.05 mg/kg/h) would provide reference data for evaluation of any pharmacodynamic effects observed at higher doses of PDC31. With a minimum of 30 min of IUP recording prior to infusion, each patient provided her own baseline (control) data for reference.

Ethical approval

The study (NCT01250587 at www.clinicaltrials.gov) was conducted at two sites in Austria (Innsbruck Medical University and Medical University of Vienna) and two in Germany (University of Mainz and University Hospital Hamburg-Eppendorf) and was approved by the national regulatory authorities and the Ethics Committee of the Medical University of Vienna for the two Austrian sites (first approval on 5 November 2010) as well as the Ethics Committee of Landesärztekammer Rheinland-Pfalz for the two German sites (first approval on 7 October 2010). Prospective study participants were identified from the participating gynecological practices, the affiliated medical schools and student communities, from referrals and through advertising in local media. Patients were enrolled, treated and followed-up from March 2011 to June 2012. Since this was a first-in-human study, patients were financially compensated for their participation in this study.

Study population

To be eligible for this study, PD patients had to have been suffering from cramping pelvic pain associated with menstruation for at least 6 months and this pain had to be at least partially responsive to non-steroidal anti-inflammatory drugs (NSAIDs) and if treated with oral contraceptives, responsive to this therapy as well. Women who were being treated with oral contraceptives at the time of recruitment were not eligible, but could be considered if therapy had been discontinued for at least 3 months prior to this study. Study participants were required to use effective birth control (excluding oral contraceptives and intrauterine devices) for the duration of the trial. Women included in the trial were at least 18 years of age and provided written informed consent prior to any screening test being performed. Women were excluded if they: had a confirmed diagnosis of pelvic inflammatory disease, endometriosis or adenomyosis; were pregnant or tested positive on the baseline rapid pregnancy test; were breastfeeding; had a fully or partially intact hymenal membrane; had clinical significant hepatic or renal function tests greater than the upper limit of normal at screening; had a clinically significant medical or psychiatric disorder within the previous 6 months which in the opinion of the treating physician would prohibit participation in the study; or had been exposed to any investigational drug within 4 weeks prior to screening.

Study procedures

Eligible prescreened patients were asked to report to their respective clinic within 8–10 h of the onset of their menstrual flow and not to take any medication (including NSAIDs) or alternative therapies after the onset of menstruation. At the time of entry, the patient had to be experiencing moderate to severe cramping pelvic pain, defined as at least 4 cm of a 10 cm maximum on a validated visual analog pain assessment scale (VAS) (Larroy, 2002). If the patient was not experiencing at least moderate pain, they were asked to re-contact the study site at the onset of their subsequent menstrual cycle. At entry, a complete physical examination, ECG and rapid pregnancy test were performed. Blood and urine samples were taken for clinical laboratory evaluation (hematology, clinical chemistry, urinalysis) and baseline pharmacokinetics. Patients were asked to assess their dysmenorrhea associated pain on the VAS at a single time point prior to start of administration of study drug.

Prior to administration of the study drug, a clean and disinfected, flexible, catheter-tip microtransducer (Unisensor 6F Pressure Sensor Tip Catheter™, Unisensor AG, Attikon, Switzerland) was placed in the uterine cavity by a trained gynecologist to collect data on intrauterine pressure (IUP) before, during and after drug infusion. These data were captured and recorded using the LabChart® Pro data acquisition software (Version 7.1.2, with Peak Analysis v1.2.1, AD Instruments GmbH, Spechbach, Germany). A minimum of 30 min baseline recording was obtained. Following this, the infusion of PDC31 was initiated and the IUP monitoring continued during the infusion and for at least 30 min after cessation of the infusion. PDC31 was diluted in 100 ml normal saline (Baxter 100 ml Viaflo Bag—0.9% sodium chloride for injection) and given as a continuous intravenous infusion over 3 h. Vital signs were measured prior to and throughout the drug infusion. An ECG was performed in the last 30 min of the drug infusion. Any spontaneously reported and clinically relevant adverse events were recorded. Women were asked to assess their dysmenorrhea pain intensity prior to drug administration and every 30 min during the infusion and at 4, 6, 8 and 12 h from the start of the infusion. Blood samples for pharmacokinetic profiling and clinical laboratory evaluation were obtained from women before, during and after the infusion. Pharmacokinetic samples were taken at baseline and at several time points during and up to 24 h after infusion. If pain was not relieved within the first hour of the infusion and the patient requested pain medication, a dose of 30 mg of regular release codeine was to be given and repeated every 4–6 h as needed while on this study. Women remained at the clinic overnight, and were discharged after 24 h following a physical examination, vital signs, pain assessment, pharmacokinetic sampling and laboratory evaluations (hematology, clinical chemistry, urinalysis). Patients were also assessed for adverse events at this time and a patient's discharge was to be delayed at the discretion of the gynecologist, pending resolution of any adverse event.

Patients were asked to return to the clinic 7 days following the infusion. At this visit, patients underwent a physical examination, vital signs and laboratory evaluations (hematology, clinical chemistry, urinalysis). The patients also had their pain assessed and were asked about any adverse events that may have occurred since their last visit. Finally, patients were contacted by telephone 30 days following drug administration to determine whether or not they have experienced any subsequent adverse events.

Outcomes

Adverse events were graded as toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.02. Any toxicity Grade 2 or greater, or one that was determined by the gynecologist to be dose-limiting and definitely, possibly or probably related to study drug, was defined as a dose-limiting toxicity. Patients who experienced a dose-limiting toxicity were to remain in the study to complete the safety evaluations and to be followed until resolution of the dose-limiting toxicity.

Clinical data were recorded using the electronic data capture system PRISM™ (version 3.0. study, produced by Nextrials Inc., San Ramon, USA). The IUP data were analyzed using an algorithm developed in MuPAD V4.0.6 (SciFace Software GmbH & Co. KG, Paderborn, Germany) and modeled on the analyses performed in other published studies evaluating IUP measures in PD (Smith, 1984, 1987; Smith and Heltzel, 1991). The algorithm analyzed the following parameters for each 15 min segment from 30 min prior to drug administration, through the infusion period and for 30 min after the infusion was stopped: Area under the curve (AUC); Number of peaks; Average peak pressure; Average contraction interval (time between contraction peaks); Contraction work (area of contraction above baseline); Linear displacement; Minimal and maximum IUP; and Minimal and maximum slope (rate of change).

IUP parameters were adjusted by a block usability factor reported on a scale of 0–100% (adjusted value = 100 * measured/block usability). Block usability refers to the portion of the 15-min segment block for which data were collected. Baseline measures were calculated as the average of the two preinfusion data time points (–30 to –15 and –15 to 0 min). Changes in uterine contractility were evaluated for each patient by comparing baseline to treatment and post-infusion periods for the parameters outlined above.

Statistical analyses

Repeated measures analysis of covariance with autoregressive covariance structure was used to assess the dose-dependency of the mean change from baseline of AUC, average peak pressure, contraction work and linear displacement and was carried out over three different time periods: 0–210 min (the complete observation period); 60–180 min; and 90–180 min.

In the second and third analyses, the 60 and 90 min starting points were selected based on pharmacokinetic considerations, to increase the likelihood of conducting the analysis during a time period of the highest plasma concentrations of PDC31. In addition, the observation period was reduced to 180 min to remove unexpectedly high variability seen in the data between 180 and 210 min following the cessation of the infusion at 180 min.

VAS change from baseline was calculated based on the changes from baseline when compared with 30 min and 1, 1.5, 2, 2.5 and 3 h during the infusion period as well as at 4, 6, 8, 12, and 24 h after the start of the infusion. The mean changes were plotted for dose groups.

All pharmacokinetic plasma samples were analyzed using a validated LC–MS/MS method. The non-compartmental pharmacokinetic parameters were calculated for each patient using WinNonlin 5.1 (Pharsight, Mountain View, USA).

There was no imputation for missing values and all calculations unless otherwise specified were performed using SAS version 9.2 or higher (SAS Institute Inc. Cary, USA). Pharmacokinetic parameters were assessed for statistical significance at a two-sided Type I error of 10% and pharmacodynamic parameters were assessed at a two-sided Type I error of 20%, limiting the chance of false-positive findings to one in five. This significance level was considered justified due to the exploratory nature of pharmacodynamic evaluations in this study.

Results

A total of 71 women were screened and from these 24 (33.8%) were enrolled. Of the 47 women not enrolled, most either withdrew consent for the study or had been screened but were not enrolled due to the completion of the study or were lost to follow-up subsequent to completing screening (55.3%). Others were in violation of either inclusion or exclusion criteria on screening. Patients were enrolled in all six dose groups with a third of the patients being treated at the highest

dose of 1 mg/kg/h. All 24 patients treated in this study were followed to the 30-day post-infusion visit (Fig. 1).

All women in this study were of reproductive age (mean 27 years, range 20–41 years) and most were Caucasian (one was Hispanic). Women were a mean height of 167.5 cm (SD 7.3 cm) and mean weight of 65.7 kg (SD 12.8 kg). Symptoms associated with PD were assessed at baseline. Most women ($n = 21$; 88%) reported severe abdominal pain at baseline. Severe pain from cramping, which may be associated with uterine contractions, was reported more frequently in the two higher dose groups of 0.5 (100%) and 1 mg/kg/h ($n = 5$; 63%).

For the primary outcome of determining the MTD, the pharmacokinetic analysis and the analysis of pain, all 24 treated patients were evaluable. However, only 12 of the 24 treated patients had valid IUP tracings for inclusion into the IUP analyses. All tracings were reviewed for inclusion by a Steering Committee member (RPS). Eight tracings (33.3%) were not considered to be valid for analysis because minimal uterine activity was detected during the 30-min baseline period, making it impossible to detect any inhibitory effect of PDC31. Two other tracings were lost due to technical difficulties (8.3%) and another two (8.3%) were considered invalid because of an increasing and non-physiological baseline pressure, indicative of technical problems with pressure capture or recording. With the exception of the 0.15 mg/kg/h group, all dose groups had at least one patient with a valid IUP tracing.

The majority ($n = 158$; 99.4%) of the protocol deviations were minor and involved incomplete laboratory tests or components of the repeat

physical exams, including deviations on the timing of recording of vital signs or VAS assessments or the taking of pharmacokinetic samples. One deviation (0.6%), however, was considered major. This occurred in the first patient dosed in this study. According to the protocol, the starting dose for this study was 0.05 mg/kg/h. The patient was mistakenly dosed at a lower dose of 0.01 mg/kg/h. Since 0.01 mg/kg/h was an approved dose level for this protocol, data for this patient were included in the final analysis for this study.

Primary outcome measure

There were no safety concerns including no dose-limiting toxicities or serious adverse events related to PDC31. In the absence of any dose-limiting toxicities, an MTD could not be declared. The MTD can be assumed to be above the 1 mg/kg/h dose.

Secondary outcome measures

IUP changes

Evaluation of the IUP parameters required adjustment for block usability in only five cases; the most common reason for obtaining < 100% usability was the interruption of the recording for patients needing to void during the IUP recording.

Overall mean change from baseline in AUC (IUP, mmHg*s) over time is displayed in Fig. 2a for all 12 patients with valid tracings (pooled across dose groups). Mean change of AUC from baseline showed a gradual

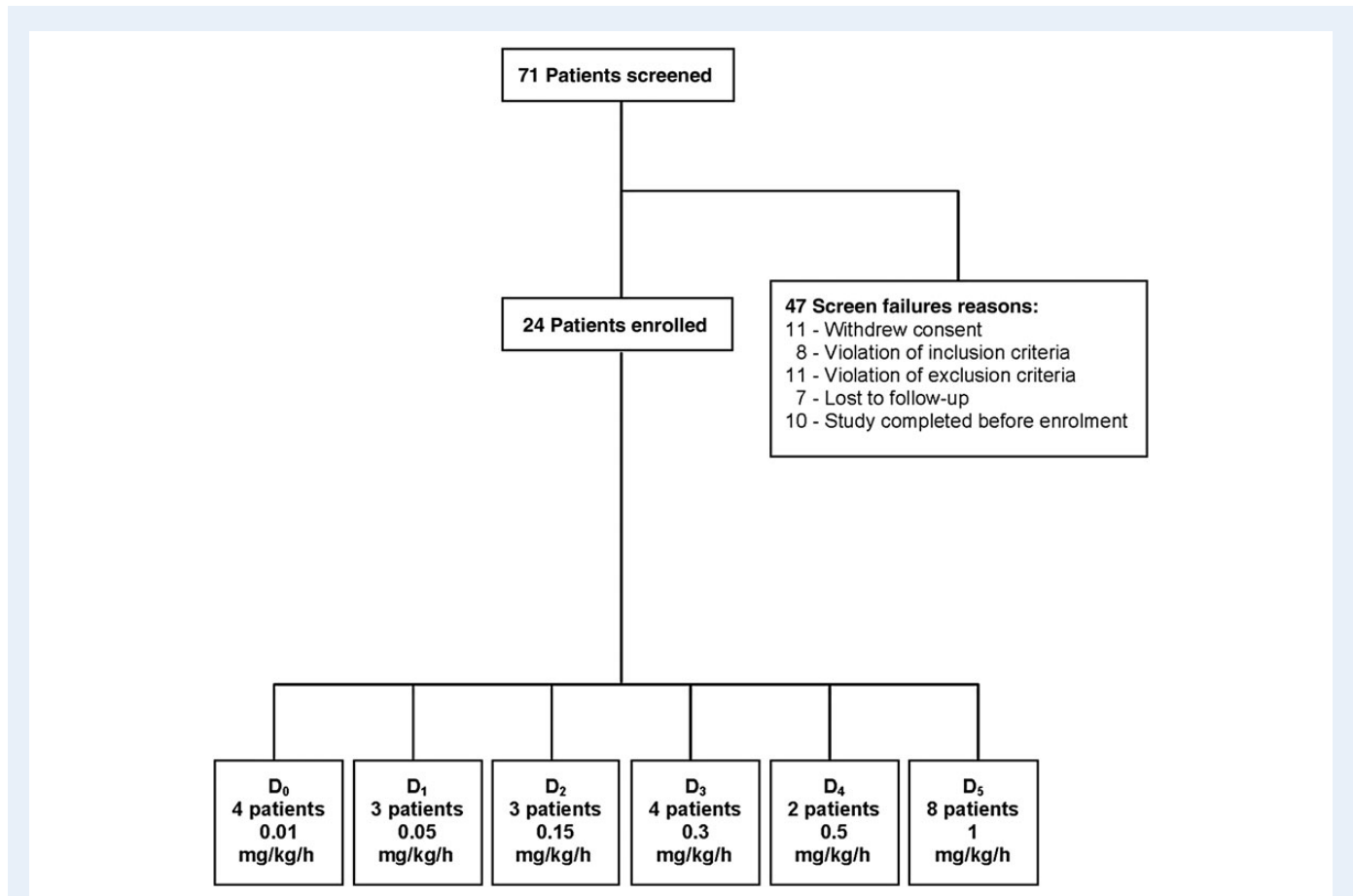


Figure 1 Screening, enrolment and treatment of patients in this study.

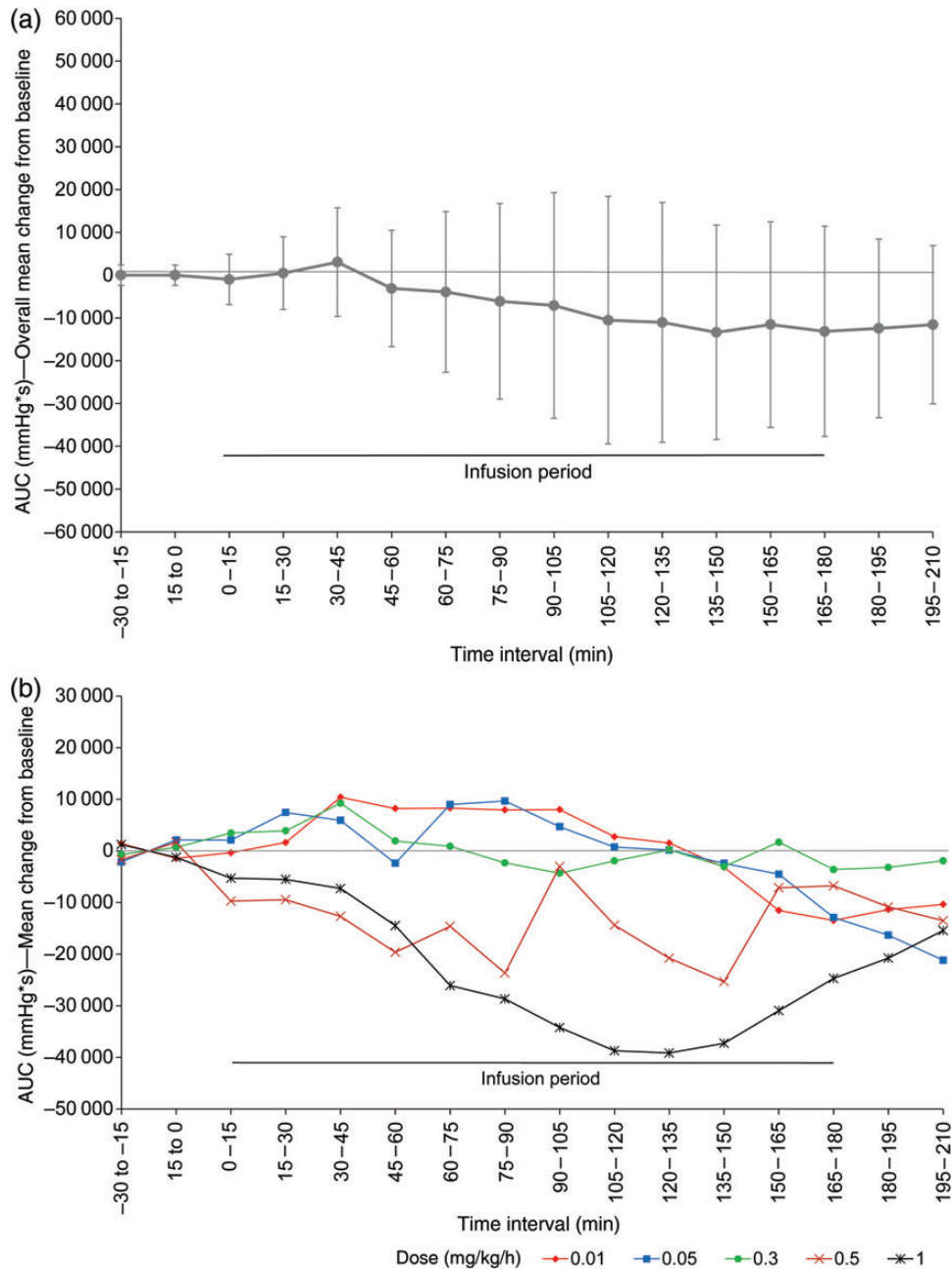


Figure 2 Change in AUC for IUP. **(a)** Overall mean change (SD) from baseline in AUC (mmHg*s) versus time interval (minutes) for the 12 patients in the IUP outcomes analysis. No valid IUP tracings were obtained for the 0.15 mg/kg/h group. The dose group 0.5 mg/kg/h had only 1 valid tracing. The infusion period was 0–180 min. Error bars represent standard deviation. **(b)** Mean change from baseline in AUC (mmHg*s) versus time interval (minutes) for the different dose groups. No valid IUP tracings were obtained for 0.15 mg/kg/h group. The dose group 0.5 mg/kg/h had only 1 valid tracing. The infusion period was 0–180 min.

decrease over the infusion period, with a maximum decrease from baseline (57 025 mmHg*s) of 13 371 mmHg*s (23%) observed at 135–150 min.

In Fig. 2b, a dose-related pattern can be seen in the meantime profiles of changes in AUC from baseline by dose. The low-dose groups of 0.01, 0.05 and 0.3 mg/kg/h do not show a consistent pattern of changes during the infusion of PDC31 (typical mean changes of no more than ± 1000 mmHg*s from baseline at each time interval). The high dose

group (1 mg/kg/h) showed a gradual decrease in IUP over the infusion period reaching a minimum of –39 127 mmHg*s (56.6%) below baseline (69 173 mmHg*s) at 120–135 min; at 180 min, the end of the post-infusion observation period, the mean change in AUC from baseline was reduced to –15 417 mmHg*s (22.3%). The pattern of AUC changes seen in the 0.5 mg/kg/h group appeared to run between the low and high dose groups and was based on an IUP tracing from a single patient.

The mean time profiles of change in the other IUP parameters of Contraction Work, Average Peak Pressure, Linear Displacement, Maximum Pressure and Minimum Pressure over time by dose group strongly resembled those seen for change in AUC from baseline (data not shown). All parameters showed a clear separation of the 1 mg/kg/h group (which shows a relatively large and consistent decrease from baseline over time) compared with the 0.01, 0.05 and 0.3 mg/kg/h groups combined (which show no notable change in these parameters over time), with the 0.5 mg/kg/h group running in between these two types of responses. Mean time profiles of change in Maximum Slope, Minimum Slope, Number of Peak and Average Contraction Interval showed less consistent dose-effects (data not shown).

In order to limit imbalance between dose groups, the dose-effect analysis of IUP parameters was limited to the analysis of four dose groups (0.01, 0.05, 0.3 and 1 mg/kg/h) where there were at least two valid IUP tracings (Table I).

Least squares (LSs) estimates of the effects of PDC31 on the changes in the four IUP parameters versus baseline, and the *P*-values from the statistical hypothesis tests are summarized in Table I. A dose-effect relationship was suggested by all four IUP parameters, based on the linear contrast over dose (*P*-values vary between 0.06 and 0.16). In addition, the mean change in AUC from baseline was statistically significant when comparing the 1 mg/kg/h and the 0.01 mg/kg/h groups (*P* = 0.12).

Finally, correlation analyses of average change from baseline in the IUP parameters AUC, Contraction Work, Average Peak Pressure and Linear Displacement observed over 60–180 min versus the pharmacokinetic parameters AUC_{3-t} and C_{max} was performed. A statistically significant correlation of change in AUC with the extent of PDC31 exposure was observed for by both AUC_{3-t} (*P* = 0.019) and C_{max} (*P* = 0.001). Similar analysis of average change in Contraction Work, Peak Pressure and Linear Displacement versus AUC_{3-t} and C_{max} identified a statistically significant correlation of these IUP parameters versus C_{max} (*P* < 0.05) and also for Contraction Work (*P* = 0.027) and Peak Pressure (*P* = 0.13) versus AUC_{3-t} , but not for Linear Displacement (*P* > 0.20).

Pain scale changes

Patients across all dose levels experienced pain relief during the 3-h infusion of PDC31, with some patients experiencing a dramatic pain reduction (>50% reduction from baseline). Mean trends in the data support a

decrease in pain over the infusion period in all dose groups and maintenance of this pain relief over a 24-h period in the higher dose groups. Figure 3 illustrates the mean changes from baseline for the different dose groups (graph initiates at 'zero' to indicate zero change from baseline prior to administration of study drug). The graph shows a clear dose differentiating effect on pain response as measured by VAS with the greatest decreases in VAS being seen in the two highest dose groups (0.5 and 1 mg/kg/h).

Four of the 24 patients received pain medication during this study under the conditions of the protocol, however, no patient received pain medication during the infusion and only one patient (1 mg/kg/h) received codeine (30 mg) on the day of the infusion.

Pharmacokinetics

The PDC31 serum concentration data (Fig. 4) demonstrated an uncomplicated, linear pharmacokinetics with: dose-proportional AUCs; a half-life between 1.7 and 2.3 h; a constant, dose-independent systemic clearance of between 72 and 124 ml/h/kg; and a 2-exponential distribution-elimination phase.

Since the infusion of PDC31 was only 3 h, the drug did not reach steady state. Based on pharmacokinetic modeling, it is estimated that the steady-state concentration would be reached after ~7–9 h and that the C_{max} at steady state would be approximately twice that achieved in this study.

Adverse events

Twelve (50.0%) of the 24 patients enrolled in this study experienced at least one adverse event. In total, 18 adverse events were recorded for this study (Table II). Of these events, 15 adverse events (83.3%) were reported as Grade 1 (mild) and 3 (16.7%) were reported as Grade 2 (moderate). Of the reported adverse events, 14 (77.8%) were considered not or unlikely related to PDC31 administration, based on the investigator assessment because the events were either pre-existing or not temporally associated with drug administration, and four (22.2%) were considered possibly related to PDC31. All but one adverse event resolved during the course of the trial. There was one serious adverse event reported (a prolongation of hospitalization due to complaints by the patient of continuing dysmenorrhea pain), which was assessed by the treating physician as not related to PDC31. This occurred 24 h following the administration of PDC31 and therefore was assumed to be related to the subject's continued PD. There were no deaths, dose-

Table I LS mean estimates of the magnitude of change of four IUP parameters by dose group and dose-effect.

| Change in parameter from baseline | LS means by dose group (mg/kg/h) | | | | P-value | | |
|-----------------------------------|----------------------------------|--------------|-------------|-----------|--------------------------|--------------------|---------------------------------|
| | 0.01 (n = 3) | 0.05 (n = 2) | 0.3 (n = 3) | 1 (n = 3) | Dose-effect: four groups | Linear dose-effect | Contrast: 1 versus 0.01 mg/kg/h |
| AUC (mmHg*s) | -353 | 6,627 | -11 107 | -26 534 | 0.236 | 0.061* | 0.116* |
| Contraction work (mmHg*s) | -6473 | -321 | -2674 | -16 171 | 0.403 | 0.163* | 0.331 |
| Average peak pressure (mmHg) | -33.0 | -8.7 | -12.5 | -79.4 | 0.297 | 0.113* | 0.253 |
| Linear displacement | -170 | 38 | 428 | -985 | 0.252 | 0.142* | 0.239 |

IUP parameters were assessed at a two-sided Type I error of 20%.

No adjustment for multiple testing was considered.

*Denotes statistical significance (*P* < 0.2).

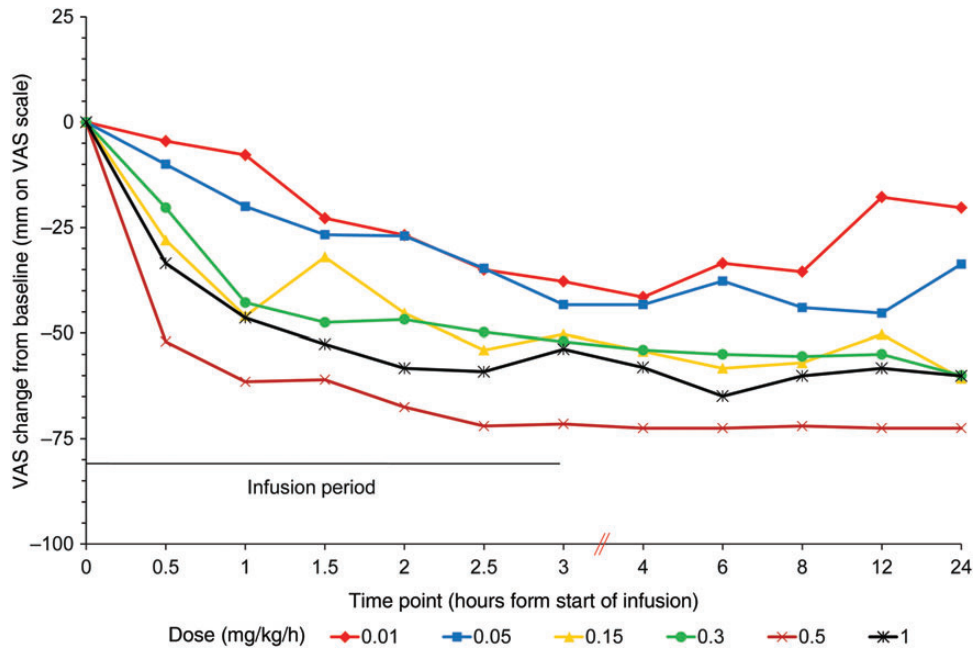


Figure 3 Absolute change from baseline in VAS pain score (means by dose group) at each time point. PDC31 infusion occurred from 0 to 3 h. The graph initiates at 'zero' to indicate zero change from baseline prior to administration of study drug. The symbol forward slash denotes time interval change on X-axis.

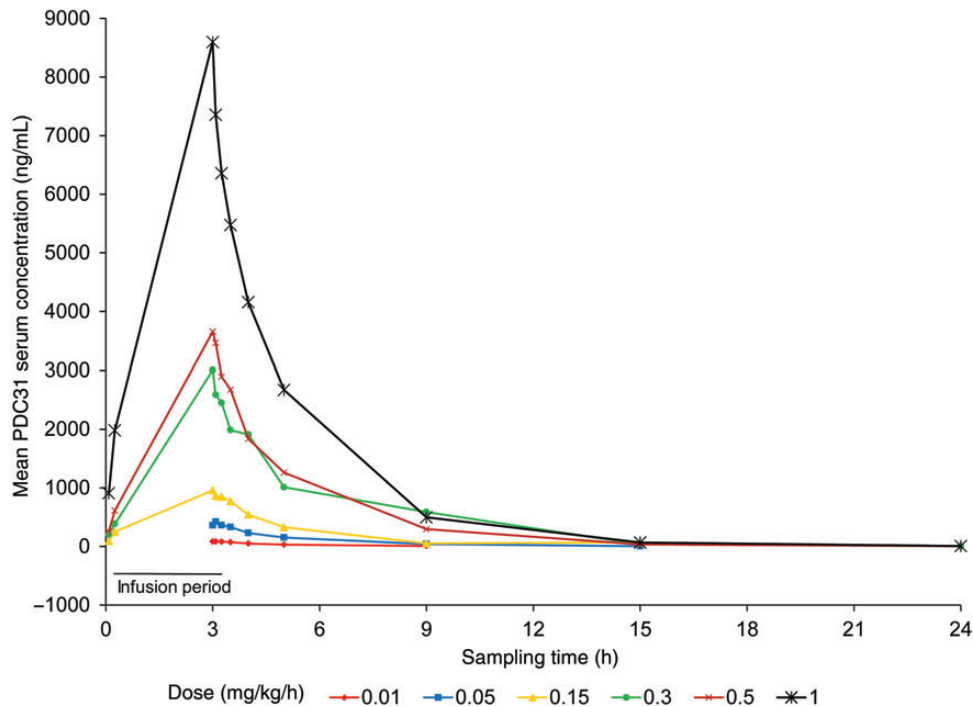


Figure 4 Mean PDC31 serum concentrations versus time (linear scale) ($n = 24$).

limiting toxicities or adverse events leading to premature discontinuation of PDC31 and only one infusion reaction (a mild hot flush) reported during this study.

Prolongations of QTc time in the ECGs which were recorded for two women at the same clinical site, dosed at 0.15 mg/kg/h were considered related to technical issues with an ECG machine which was subsequently

Table II Adverse events.

| Dose cohort (mg/kg/h) | Adverse event | Grade 1 (Mild), N (%) | | Grade 2 (Moderate), N (%) | | Total, N (%) | | Total patient population (N (%)), x/n (%) |
|--------------------------|--|--------------------------|-----------|------------------------------|----------|--------------|-----------|---|
| | | R | NR | R | NR | R | NR | |
| All doses | | 4 (22.2) | 11 (61.1) | 0 (0.0) | 3 (16.7) | 4 (22.2) | 14 (77.8) | 18 (100) 12/24 (50.0) |
| 0.01 (n = 4) | Hypotension | | 1 (5.6) | | | 1 (5.6) | 3 (16.7) | 4 (22.2) |
| | Hot flush | 1 (5.6) | | | | | | 3/4 (75.0) |
| | Diarrhea | | 1 (5.6) | | | | | |
| | Headache | | 1 (5.6) | | | | | |
| 0.05 (n = 3) | Fatigue | 1 (5.6) | | | | 1 (5.6) | | 1 (5.6) 1/3 (33.3) |
| 0.15 (n = 3) | QTc prolongation during ECG ^a | | 1 (5.6) | | 1 (5.6) | | 2 (11.1) | 2 (11.1) 2/3 (66.7) |
| 0.3 (n = 4) | Subclinical urinary infection | | 1 (5.6) | | | | 2 (11.1) | 2 (11.1) |
| | Platelet count increased | | 1 (5.6) | | | | | 2/4 (50.0) |
| 0.5 (n = 2) | | | | | | | | 0 (0.0) |
| 1 (n = 8) | Hypertension | | 1 (5.6) | | | 2 (11.1) | 7 (38.9) | 9 (50.0) |
| | Lymphocytosis | | 1 (5.6) | | | | | 4/8 (50.0) |
| | Severe pain due to dysmenorrhea ^b | | 1 (5.6) | | | | | |
| | Blood bilirubin increased | | 1 (5.6) | | | | | |
| | Platelet count increased | | 1 (5.6) | | | | | |
| | Nausea ^c | | | | | 1 (5.6) | | |
| | Headache ^c | 1 (5.6) | | | | | | |
| | Dizziness ^c | 1 (5.6) | | | | | | |
| | Hypothyroidism ^c | | | | 1 (5.6) | | | |

R, related; NR, not related; x, number of patients with adverse events reported; n, number of patients in cohort; N, number of adverse events.

^aFindings were likely due to an artifact based on unreliability of the ECG machine.

^bDeclared a serious adverse event because patient remained in hospital beyond the 24 h follow-up.

^cHypothyroidism diagnosis was made in this patient following the study but symptoms preceded the study.

replaced. There were no further post-treatment reports of QTc prolongation, even at higher doses of PDC31, suggesting these observations were not related to PDC31 treatment.

Discussion

The primary objective of the study was to determine a safe and effective dose range for PDC31 by determining the MTD of PDC31 in otherwise healthy patients with PD. The dose of PDC31 was escalated to 1 mg/kg/h and in the absence of any dose-limiting toxicity, MTD could not be declared.

This finding was not unexpected since for targeted therapies, the pharmacodynamic effects are often realized at doses much lower than those associated with toxicity. Furthermore, based on the putative mechanism of action of PDC31 as an allosteric modulator of the PGF_{2α} receptor, the effect of PDC31 is likely greater in the presence of high concentrations of PGF_{2α} (as is the case with PD). Binding of PDC31 to a site distinct from where PGF_{2α} binds is expected to alter the signal transduced by PGF_{2α} binding, converting the PGF_{2α} receptor from a contractile receptor to a relaxatory one. The design of the study anticipated the potential for this result and therefore pharmacodynamic outcome measures (IUP and PD associated pain) were included as secondary objectives. However, this was a first-in-human study and exposure to PDC31 was limited for safety reasons. The secondary parameters were intended

to provide additional information for the dose finding and demonstrated significance at a Type I error rate of 20%, appropriate for a study at this early stage of development. The data obtained support the hypothesis of a dose-dependent effect of PDC31 on IUP and pain. While the IUP data are limited, the change in mean AUC in the 1 mg/kg/h dose group compared with the lowest dose groups suggests an effect of PDC31. This is supported by the pharmacokinetic/pharmacodynamic correlation, specifically the correlation of AUC_{3–t} and C_{max} with the IUP AUC (mmHg*s) during the 60–180 min interval. The pain data are consistent with the IUP findings, suggesting pain relief associated with reduction in uterine contractility. Relief of pain reported in patients in the 0.5 mg/kg/h dose group is consistent with the reduction in IUP observed in the one valid IUP tracing obtained at this dose level.

While the pain data may be considered subjective and no placebo group was included in this trial, it should be noted that pain measured using the VAS is routinely used as the primary end-point in the study of drugs for the treatment of PD. The decrease observed in this trial is greater than that reported in placebo groups of other studies of patients with PD (Smith and Powell, 1987). Valentin et al. reported that in 18 PD patients given an intravenous injection of either placebo or atosiban within 26 h of the onset of menstruation, no effect of atosiban or placebo on VAS pain scores or IUP was found during a 90 min monitoring interval where VAS scores were assessed every 15 min (Valentin et al., 2000).

The IUP changes found in this study are consistent with those of previous studies of NSAIDs where placebo treatment was associated with increases in the measured IUP parameters by roughly 20%, while treatment resulted in reductions of 50–60% or more, similar to what was observed at the high dose level of PDC31 (Smith and Powell, 1982; Smith and Heltzel, 1991).

Adverse events experienced in this study were mild (15 of 18 adverse events, i.e. 83.3%) and many were not considered to be associated with PDC31 (77.8%) but rather associated symptoms of PD. Only one serious adverse event occurred which was not considered to be related to PDC31, but resulting from the patient's underlying condition. This supports the safety of PDC31 up to doses of 1 mg/kg/h.

The pharmacokinetic profile of PDC31 is uncomplicated, linear and suggests dose proportionality. The half-life of PDC31 was ~2 h. As such, it is estimated that steady-state concentrations of the drug would only be reached after 7–9 h of infusion and therefore were not achieved in this study. From the pharmacokinetic profiles, it is expected that the true C_{max} at steady state would be in the order of two times that of the C_{max} values reported for each dose level in this study. Therefore, C_{max} levels of the 1 mg/kg/h dose level would be similar to steady-state levels from a continuous infusion at the 0.5 mg/kg/h dose level. If an extended infusion period (e.g. 24–48 h) is planned for future clinical studies, it will be important to collect further safety and pharmacokinetic information at steady state concentrations.

The data from this study support further development of PDC31 as a treatment for PD and preterm labor. While an intravenous formulation of PDC31 is ideal in the treatment of preterm labor where a rapid effect is required, a non-parenteral formulation of the drug would be more suitable for the treatment of PD. The 1 mg/kg/h dose appears to be safe and potentially effective in reducing IUP and pain associated with excessive uterine contractility when given as a 3-h infusion.

Authors' roles

All authors listed were substantial contributors to the design and implementation of this study as well as the interpretation of the analysis of the data. In addition, all authors critically reviewed and contributed to the development of this article and approved the final version.

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Conflict of interest

B.B., R.M.L., L.W., R.J.S., K.J.B. and C.F.S. received reimbursement for the conduct of this study from PDC Biotech GmbH. W.H., M.S., B.J. and R.P.S. are paid consultants for PDC Biotech GmbH. P.G. is a paid consultant and shareholder of PDC Biotech GmbH.

References

- Friel A, O'Reilly MW, Sexton DJ, Morrison JJ. Specific PGF_{2α} receptor (FP) antagonism and human uterine contractility in vitro. *BJOG* 2005; **112**:1034–1042.
- Goupil E, Tassy D, Bourguet C, Quiniou C, Wisehart V, Pétrin D, Le Guill C, Devost D, Zingg HH, Bouvier M et al. A novel biased allosteric compound inhibitor of parturition selectively impedes the PGF_{2α}-mediated Rho/Rock signalling pathway. *J Biol Chem* 2010; **285**:25624–25636.
- Hirst JJ, Parkington HC, Young R, Palliser HK, Peri KG, Olson DM. Delay of preterm birth in sheep by THG11331, a prostaglandin F_{2α} receptor antagonist. *Am J Obstet Gynecol* 2005; **193**:256–266.
- Larroy C. Comparing visual-analog and numeric scales assessing menstrual pain. *Behav Med* 2002; **27**:179–181.
- Roth-Brandel U, Bygdman M, Wiquist N. Effect of intravenous administration of prostaglandin E1 and F_{2a} on the contractility of the non-pregnant women uterus in vivo. *Acta Obstet Gynecol Scand* 1970; **49**:19.
- Sales KJ, Jabbour HN. Cyclooxygenase enzymes and prostaglandins in pathology of the Endometrium. *Reproduction* 2003; **126**:559–567.
- Schulz M, Chung-Hun St.C. Review and comparison of traditional Phase I clinical trial designs and the continual reassessment method in cancer research. *ScianNews* 1994; **4**:1–4.
- Smith RP. Intrauterine pressure analysis in nonpregnant dysmenorrheic women. *Med Instrum* 1984; **18**:137–139.
- Smith RP. The dynamics of nonsteroidal anti-inflammatory therapy for primary dysmenorrhea. *Obstet Gynecol* 1987; **70**:785–788.
- Smith RP, Heltzel J. Interrelation of analgesia and uterine activity in women with primary dysmenorrhea. *J Reprod Med* 1991; **36**:260–264.
- Smith RP, Powell JR. Intrauterine pressure changes during dysmenorrhea therapy. *Am J Obstet Gynecol* 1982; **143**:286–292.
- Smith RP, Powell JR. Simultaneous objective and subjective evaluation of meclofenamate sodium in the treatment of primary dysmenorrhea. *Am J Obstet Gynecol* 1987; **157**:611–616.
- Valentin L, Sladkevicius P, Kindahl H, Broeders A, Marsal K, Melvin P. Effects of a vasopressin antagonist in women with dysmenorrhea. *Gynecol Obstet Invest* 2000; **50**:170–177.