ZY5301 Tablet vs Placebo for Treatment of Chronic Pelvic Pain After Pelvic Inflammatory Disease
A Phase 2 Randomized Clinical Trial

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Abstract

IMPORTANCE Chronic pelvic pain (CPP) is the main sequela of pelvic inflammatory disease (PID), with no established treatment. ZY5301 tablets, an effective part preparation extracted from Ajuga decumbens Thunb. (jingucao), are being tested as a treatment for CPP caused by PID.

OBJECTIVE To evaluate whether ZY5301 tablets are effective and safe for CPP treatment in women with PID.

DESIGN, SETTING, AND PARTICIPANTS This placebo-controlled double-blind, dose-parallel, phase 2 randomized clinical trial was conducted in 9 hospitals in China. Female participants with CPP after PID were enrolled between October 16, 2020, and August 31, 2021. The data analysis was performed between December 2021 and March 2022.

INTERVENTIONS Participants were randomized 1:1:1 to receive ZY5301 300 mg/d, ZY5301 600 mg/d, or placebo orally 3 times a day for 12 weeks.

MAIN OUTCOMES AND MEASURES Visual analog scale (VAS) scores were the main measure used to evaluate the efficacy of ZY5301 in reducing CPP. The evaluation end points for VAS score included changes in mean weekly VAS score from baseline, area under the VAS score-time curve, pain remission (VAS score of 0 and 1) rate, and median time to pain remission. Safety was evaluated by the occurrence of treatment-emergent and treatment-related adverse events.

RESULTS In total, 180 women were randomly assigned, and 177 were included in the efficacy analysis; thus, the full analysis set included 60 participants in the ZY5301 mg/d group (mean [SD] age, 37.4 [8.1] years), 58 in the ZY5301 600 mg/d group (mean [SD] age, 37.1 [7.9] years), and 59 in the placebo group (mean [SD] age, 38.9 [7.3] years). Participant characteristics at baseline were similar among the groups. After 12 weeks of treatment, the mean (SD) change in VAS score from the baseline was −2.1 (1.7) points, −3.5 (1.5) points, and −3.8 (1.7) points in the placebo, ZY5301 300 mg/d, and ZY5301 600 mg/d groups, respectively (P < .001). The pain remission rates at week 12 were 43.3% and 53.5% in the ZY5301 300 mg/d and ZY5301 600 mg/d groups, respectively, a significant difference compared with the placebo group (11.9%; P < .001). All the other end points showed similar improvements. The ZY5301 600 mg/d group had better efficacy than the ZY5301 300 mg/d group, but the difference was not significant. The safety analysis revealed no significant differences among groups.

CONCLUSIONS AND RELEVANCE These findings show that ZY5301 tablet is efficacious for the relief of CPP with acceptable tolerability.

Key Points

Question What is the efficacy of ZY5301 tablets for treating chronic pelvic pain (CPP) caused by pelvic inflammatory disease in women?

Findings In this phase 2 randomized clinical trial in 180 women treated with ZY5301 300 mg/d, ZY5301 600 mg/d, or placebo, CPP significantly improved after 12 weeks of ZY5301 treatment, with a statistically meaningful difference compared with placebo. Safety evaluation revealed no significant differences among groups.

Meaning These findings show that ZY5301 tablet has a good safety profile and promising efficacy in the relief of CPP caused by pelvic inflammatory disease.
Abstract (continued)

TRIAL REGISTRATION  ClinicalTrials.gov Identifier: NCT05460546

Introduction

Pelvic inflammatory disease (PID) is a common reproductive health condition among women of reproductive age. It refers to the infection-induced inflammation of the upper female genital tract and includes any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis.1-3 In the US, approximately 1 million women experience PID annually, and approximately 2.5 million women of reproductive age have had a PID diagnosis.4

Improper or inadequate treatment may increase the risk of serious potential sequelae of PID.5 Between 10% and 20% of women with PID are subsequently infertile, and 40% develop chronic pelvic pain (CPP).6 The Pelvic Inflammatory Disease Evaluation and Clinical Health study showed that nearly one-third of women with PID developed CPP after 3 years of follow-up and that more than one-half experienced highly intense pain.7 In addition to bodily pain, women with CPP concurrently experience reductions in physical function, general health, vitality, social functioning, and mental health.8

The management of CPP is difficult as no established treatments are available.9,10 Chronic pelvic pain is not associated with an infectious inflammation; thus, it is not sensitive to antibiotic treatment. Finite evidence has supported the use of nonsteroidal anti-inflammatory drugs,11 tricyclic antidepressants,12,13 gabapentin,14 and serotonin-norepinephrine reuptake inhibitors15,16 for CPP, while evidence-based therapy still remains limited.

Ajuga decumbens Thunb. (jingucao) is a medicinal plant native to China that is popularly used to treat chronic pelvic inflammation and hysteromyoma. Its main bioactive components are iridoid glycosides, such as 8-O-acetylharpagide and harpagide, which have antibacterial, anti-inflammatory, and antiviral activities.17 Jincaopian (ZY5301) is an effective part preparation extracted from A decumbens Thunb., which is rich in iridoid glycosides. Pharmacologic studies have shown that ZY5301 can significantly inhibit the increase in uterine swelling caused by chronic PID in rats and significantly inhibits pathologic changes, such as endometrial glandular epithelial hyperplasia, thickening, and inflammatory infiltration (Jianrong Li, PhD, unpublished data, 2012). In pharmacokinetics studies in rats, results showed that the iridoid glycosides were quickly absorbed orally in a dose-dependent manner.18

A 9-month oral toxicity study of ZY5301 in beagles showed that the no observed adverse effect level dose was 80 mg/kg per day. In the phase 1 clinical trial, the safety of ZY5301 single and multiple administration was evaluated, and a maximum daily dose of 1200 mg was recommended for the phase 2 clinical trial. The data from the phase 1 trial were submitted in November 2019 to the China National Medical Products Administration in application for a phase 2 clinical trial of ZY5301, which was approved in March 2020. In this study, we evaluate the efficacy and safety of ZY5301 in the treatment of women with CPP caused by PID.

Methods

Trial Design and Oversight

This multicenter, placebo-controlled, double-blind, dose-parallel, phase 2 randomized clinical trial was performed in accordance with the principles of the Declaration of Helsinki and the guidelines of Good Clinical Practice.19 The study protocol and statistical analysis plan are provided in Supplement 1. Ethical approval was obtained by the institutional review board or ethics committee at each investigational site before trial initiation. Patients were enrolled by their clinicians after providing
written informed consent. Data analysis and reporting were performed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

The trial was performed in 9 centers in China (eAppendix 1 in Supplement 2). Trial enrollment began on October 16, 2020, and was completed on August 31, 2021. The investigators conducted the trials, gathered the data, inputted the data, and maintained the trial database using an electronic data capture system; they were masked to the interventions. Beijing Konruns Pharmaceutical Co Ltd provided the trial drugs, the packages of which were prelabeled by a local Chinese company, Zhi Zhi Medicine. Zhi Zhi Medicine also assisted with data management and the statistical analysis.

**Trial Participants**

The diagnostic criteria of CPP caused by PID for this study are based on the 9th edition of Chinese Obstetrics and Gynecology and the guidelines for CPP published by the American Association of Obstetricians and Gynecologists. Eligible participants were women aged 18 to 55 years who fulfilled the clinical diagnostic criteria for PID, had nonperiodic lower abdominal or pelvic pain for at least 6 months, and met all of the following inclusion criteria: (1) sexually active, (2) visual analog scale (VAS) scores before enrollment of at least 4 points, (3) McCormack scale scores between 4 and 12 points, (4) use or willingness to use contraception to avoid pregnancy, and (5) no obvious pelvic pathology by transvaginal ultrasound examination.

The key exclusion criteria were as follows: (1) acute onset of PID; (2) pregnant, lactating or planning to become pregnant during the trial and within 3 months after the trial; (3) diagnosis of gynecologic tumors, trichomonas vaginitis, vulvovaginal candidiasis, bacterial vaginosis, acute cervicitis, endometriosis, adenomyosis, and other conditions with similar symptoms; (4) previous diagnosis of cervical intraepithelial neoplasia, primary or secondary dysmenorrhea, or pelvic stasis syndrome and CPP caused by other non-PIDs; (5) serum cancer antigen 125 or erythrocyte sedimentation rate greater than 1.5 times the upper limit of normal (ULN); and (6) liver function (alanine aminotransferase or aspartate aminotransferase) or routine blood test (red blood cell count, white blood cell count, hemoglobin, or blood platelet count) results greater than 1.5 times the ULN and kidney function (serum creatine) greater than the ULN. Additional exclusion criteria are provided in eAppendix 2 in Supplement 2.

**Trial Procedures**

After a 1- to 2-week screening and lead-in period, eligible patients were randomly assigned 1:1:1 to receive placebo, ZYS301 300 mg/d, or ZYS301 600 mg/d, and all tablets were identical in appearance and taken 3 times a day for 12 weeks. Participants were assessed within 3 days prior to treatment initiation (visit 0) and as follows: visit 1, day 28 ± 4; visit 2, day 56 ± 4; visit 3, day 84 ± 4; and follow-up, 4 weeks (±4 days) after termination of treatment. Treatment efficacy, adverse events (AEs), and safety assessments were recorded throughout the trial. Participants were not allowed to use other drugs (eg, antibiotics, nonsteroidal anti-inflammatory drugs, antidepressants, and hormone drugs) or treatment methods that could affect the efficacy evaluation (including acupuncture and moxibustion, cupping, scraping, and other traditional Chinese medicine therapies).

**Randomization and Masking**

The randomization sequence was generated by an independent statistician using SAS, version 9.4 software (SAS Institute, Inc). The participant and drug numbers were all unique and corresponded to each other and were handled independently by the designated statistician. Additionally, confidentiality was maintained for the clinician and participants.

The drug with the code was allocated to the patient after signed informed consent and agreement to participate. Allocation concealment was maintained by masking the participants, investigators, clinicians, and statisticians until study completion.
End Points
The VAS score was the main measure used to evaluate the efficacy outcome. The VAS score ranges from 0 to 10, with higher scores indicating greater pain intensity. During the study period, participants evaluated the degree of pain in the past 24 hours every night before going to bed and recorded the worst pain score of the day. The VAS scores in this study are accurate to 1 decimal place.

The mean VAS score for a week was calculated by dividing the sum of the scores for each day of the week by the number of days the score was recorded (missing scores were not filled in). The mean VAS score at 1 week during the lead-in period was used as the baseline. During the treatment period, if the number of recorded days in a certain week was less than 4, the mean VAS score for that week was recorded as missing. Pain remission was considered as a VAS score of 0 to 1 point and no longer greater than or equal to 2 points at any subsequent evaluation. The pain remission rate was defined as the proportion of patients who achieved pain remission after treatment.

The evaluation end points for the VAS score included changes in VAS weekly mean score from baseline to week 12 among groups and the differences in the area under the VAS score-time curve, pain remission rate, and pain remission time among groups. Other outcome measures included the Short Form-12 (SF-12) scale (0-100, with higher scores indicating better physical and mental health) and McCormack scale (0-3, with higher scores indicating greater gynecologic pain) (eMethods in Supplement 2). In addition to evaluating preliminary efficacy and safety of ZYS301, we evaluated the primary efficacy end point and optimal treatment dosage for the phase 3 clinical trial.

Treatment-emergent AEs (TEAEs) and treatment-related AEs (TRAEs) were recorded throughout the trial. Treatment-emergent AEs refer to any AE that occurs on or after the first use of the investigational drug, regardless of whether it is related to the treatment. Treatment-related AEs refer to any TEAE related to the treatment. The severity of TEAEs and TRAEs was assessed according to Common Terminology Criteria for Adverse Events, version 5.0.21 Safety evaluations included various concerns after drug treatment, vital signs, laboratory evaluations, and physical and gynecologic examinations. At each visit, the participants were also asked about their menstrual status (including changes in menstrual cycle, menstrual period, and menstrual volume vs previous menstrual periods).

Statistical Analysis
The data analysis was performed between December 2021 and March 2022. Efficacy was analyzed mainly in the full analysis set (FAS). The FAS population included all participants who were randomized, received at least 1 dose of the investigational drug or placebo, and had valid assessments after baseline. For continuous variables, mean (SD) and median (range) are reported. For categorical variables, counts with percentages are reported.

The scores of the various scales (VAS, SF-12, and McCormack) at different visit points and their changes compared with baseline were calculated. The change in scale scores compared with baseline was performed using paired t test or Wilcoxon signed rank test. The difference in scale scores was compared among groups using analysis of variance or Kruskal-Wallis tests. If there was statistical significance in the overall comparison among groups, the Bonferroni method or the covariance model was used for pairwise comparison, and the pairwise comparison differences and 95% CIs were calculated. Missing data were imputed using the last observation carried forward method.

All statistical analyses were conducted using SAS, version 9.4 (SAS Institute). Statistical significance was defined as P < .05 with 2-sided testing.

Results
Participants
A total of 251 patients were screened, of whom 180 were eligible for participation and underwent randomization at a 1:1:1 ratio, with 60 patients assigned to each group (Figure 1). Three patients (1.7%) were lost to follow-up and had no valid data after treatment (2 patients in the ZYS301 600
mg/d group and 1 patient in the placebo group). The FAS population included 60 patients in the ZYS301 300 mg/d group (mean [SD] age, 37.4 [8.1] years), 58 in the ZYS301 600 mg/d group (mean [SD] age, 37.1 [7.9] years), and 59 in the placebo group (mean [SD] age, 38.9 [7.3] years). All patients in the FAS population were included in the efficacy analysis. The characteristics of included patients at baseline were similar among groups (Table 1).

**VAS Scores**

The results based on VAS scores in the FAS population are shown in Table 2 and Figure 2. The mean (SD) VAS scores at baseline were 5.0 (0.8) cm in the placebo group, 5.0 (0.6) cm in the ZYS301 300 mg/d group, and 5.1 (0.8) cm in the ZYS301 600 mg/d group. After 12 weeks of treatment, the mean (SD) changes in VAS scores from baseline were −2.1 (1.7) cm, −3.5 (1.5) cm, and −3.8 (1.7) cm in the placebo, ZYS301 300 mg/d, and ZYS301 600 mg/d groups, respectively. There was a statistically significant difference between the active treatment groups and the placebo group (P < .001), but not between 300 mg/d and 600 mg/d groups. A summary of all VAS scores by week for both the FAS and per-protocol set is shown in Table 1 in Supplement 2.

The change in the weekly VAS scores is shown in Figure 2A. The mean (SD) areas under the VAS score-time curve after 12 weeks of treatment were 194.1 (85.6) cm-week in the 600 mg/d group, 215.0 (99.5) in the 300 mg/d group, and 282.4 (107.7) cm-week in the placebo group, with significant differences among the 3 groups (P < .001) (Table 2).

Pain remission was achieved by 11.9% of patients (7 of 59) in the placebo group, 43.3% (26 of 60) in the 300 mg/d group, and 53.5% (31 of 58) in the 600 mg/d group (P < .001) (Figure 2B). The median time to pain remission was shorter for patients treated with ZYS301 600 mg/d (68 days; 95% CI, 60.0-83.0 days), compared with either the placebo (>84 days) or ZYS301 300 mg/d (84

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**Table 1. Participant Baseline Characteristics (Full Analysis Set)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo group (n = 59)</th>
<th>ZYS301 group (n = 60)</th>
<th>ZYS301 group (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>38.9 (7.3)</td>
<td>37.4 (8.1)</td>
<td>37.1 (7.9)</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>161.9 (4.7)</td>
<td>161.0 (4.5)</td>
<td>160.8 (4.6)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>58.7 (6.5)</td>
<td>58.5 (8.3)</td>
<td>58.1 (6.6)</td>
</tr>
<tr>
<td>CA-125, median (IQR), U/mL</td>
<td>12.2 (8.7-18.4)</td>
<td>11.9 (9.3-16.4)</td>
<td>11.6 (9.3-15.9)</td>
</tr>
<tr>
<td>ESR, median (IQR), mm/h</td>
<td>8.0 (5.0-13.0)</td>
<td>8.0 (5.0-11.0)</td>
<td>9.0 (6.0-11.0)</td>
</tr>
<tr>
<td>Alcohol use disorder, No. (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drug use disorder, No. (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Menstrual cycle, mean (SD), d</td>
<td>30.3 (9.3)</td>
<td>28.5 (3.4)</td>
<td>30.2 (7.5)</td>
</tr>
<tr>
<td>VAS score, mean (SD), cm</td>
<td>5.0 (0.8)</td>
<td>5.0 (0.6)</td>
<td>5.1 (0.8)</td>
</tr>
</tbody>
</table>

Abbreviations: CA-125, cancer antigen 125; ESR, erythrocyte sedimentation rate; VAS, visual analog scale.

* The VAS was used to evaluate the intensity of chronic pelvic pain. Scores range from 0 to 10 cm, with higher scores indicating greater pain intensity.
days; 95% CI, 74.0 to not reached; P < .001) (Table 2, Figure 2C). During the 4-week follow-up period after termination of treatment, the pain recurrence rate remained low at 1 of 16 patients evaluated in the 300 mg/d group, 1 of 15 evaluated in the 600 mg/d group, and 0 of 4 evaluated in the placebo group.

**SF-12 and McCormack Scales**

Compared with the baseline, both the mental component score (MCS) and physical component score (PCS) of the SF-12 showed significant improvements in the ZY5301 600 mg/d group (mean [SD], 44.4 [9.5] vs 49.2 [8.2] and 46.5 [6.4] vs 49.9 [6.6] points, respectively; P < .001) and the ZY5301 300 mg/d group (mean [SD], 45.5 [7.3] vs 50.1 [6.5] and 46.5 [7.6] vs 50.3 [5.76] points, respectively; P < .001) and for PCS in the placebo group (mean [SD], 45.4 [6.3] vs 49.0 [7.4] points; P < .001) (eTable 2 in Supplement 2). However, the MCS and PCS improvement between the treatment groups and the placebo group was not statistically different.

Similarly, significant improvements from baseline in the McCormack total score at week 12 also occurred in the ZY5301 600 mg/d group (mean [SD], 7.0 [2.2] vs 1.6 [1.9] points; P < .001), ZY5301 300 mg/d group (mean [SD], 6.7 [2.1] vs 1.6 [1.9] points; P < .001), and placebo group (mean [SD], 7.0 [2.4] vs 3.5 [2.6] points; P < .001). Rebound pain of the McCormack scale in the ZY5301 600 mg/d group was not significant (eTable 2 in Supplement 2). Only improvement in the gynecologic examination score was statistically different between the ZY5301 600 mg/d (mean [SD], 4.9 [1.5] vs 1.1 [1.3] points) and 300 mg/d (mean [SD], 4.7 [1.5] vs 1.1 [1.3] points) groups and the placebo group (mean [SD], 4.8 [1.6] vs 2.6 [2.0] points) (P < .001) but not between the ZY5301 300 mg/d and 600 mg/d groups. The results of pairwise comparisons among the 3 groups are shown in eTable 3 in Supplement 2.

**Safety**

TEAEs were recorded for 21 participants (36.2%) in the ZY5301 600 mg/d group, 23 (38.3%) in the ZY5301 300 mg/d group, and 17 (28.8%) in the placebo group, and no statistical difference was observed (Table 3). TRAEs in these groups were recorded in 2 participants (3.5%), 1 participant (1.7%), and 3 participants (5.1%), respectively. All SAEs were judged by the investigators to be unrelated to the treatment. In addition, no significant changes were observed in the menstrual cycle of participants in each group.

### Table 2. Summary of the Change of VAS Scores at Week 12 (Full Analysis Set)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo group (n = 59)</th>
<th>ZY5301 group 300 mg/d (n = 60)</th>
<th>ZY5301 group 600 mg/d (n = 58)</th>
<th>P value among the 3 groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score</td>
<td>Change from baseline</td>
<td>Score</td>
<td>Change from baseline</td>
</tr>
<tr>
<td>VAS score, mean (SD), cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.0 (0.8)</td>
<td>NA</td>
<td>5.0 (0.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Week 4</td>
<td>3.6 (1.6)</td>
<td>−1.4 (1.7)</td>
<td>3.3 (1.7)</td>
<td>−1.7 (1.7)</td>
</tr>
<tr>
<td>Week 8</td>
<td>3.2 (1.5)</td>
<td>−1.8 (1.7)</td>
<td>2.5 (1.6)</td>
<td>−2.5 (1.6)</td>
</tr>
<tr>
<td>Week 12</td>
<td>2.9 (1.5)</td>
<td>−2.1 (1.7)</td>
<td>1.6 (1.4)</td>
<td>−3.5 (1.5)</td>
</tr>
<tr>
<td>Pain remission rate, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>3 (5.1)</td>
<td>NA</td>
<td>5 (8.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Week 8</td>
<td>5 (8.5)</td>
<td>NA</td>
<td>12 (20.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Week 12</td>
<td>7 (11.9)</td>
<td>NA</td>
<td>26 (43.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Area under the VAS score-time curve, mean (SD), cm·wk</td>
<td>282.4 (107.7)</td>
<td>NA</td>
<td>215.0 (99.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Time to pain remission, median (95% CI), d</td>
<td>NA</td>
<td>NA</td>
<td>84.0 (74.0 to not reached)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; VAS, visual analog scale.

a Scores range from 0 to 10 cm, with higher scores indicating greater pain intensity.
b P < .05 vs baseline using Wilcoxon signed rank test.
c P < .001 vs baseline using Wilcoxon signed rank test.
d Differences compared using Kruskal-Wallis test.
e Differences in the pain remission rate were compared using Cochran-Mantel-Haenszel χ² method, and the differences in time to pain remission were compared using log-rank χ² method.
Discussion

In this randomized clinical trial, the ZY5301 600 mg/d dose was determined based on one-half the maximum daily dose from the phase 1 clinical study (ie, 1200 mg/d). Based on the pharmacokinetics data of ZY5301 in rats and the folk medication regimen of A decumbens Thunb. in China, 3 times a day was selected as the dosing regimen. The intervention period (12 weeks) was determined to be long enough to exhibit efficacy in treatment of CPP based on previous clinical studies. In terms of efficacy measures, the weekly VAS score mean was calculated because CPP can fluctuate during a woman's menstrual cycle, so eliciting a pain score at a single time point is unlikely to capture the effect of ZY5301 tablets or reflect the woman's experience of pain.

As in other clinical trials, our trial findings showed a potential placebo effect, with mean (SD) changes of VAS scores from the baseline of −2.07 (1.67; \( P < .001 \)). Under this circumstance, the clinical efficacy of ZY5301 tablets has been further confirmed. Different from the indicator of the change from baseline in VAS score, the definition of pain remission included not only pain improvement but also clinical cure (defined as a VAS score of 0-1 points and no longer \( \geq 2 \) points). Consequently, the proportion of women with a clinical cure may better reflect the efficacy of ZY5301 tablets in routine clinical care. At week 12 in our study, the ZY5301 300 mg/d and 600 mg/d groups were significantly better than the placebo group in terms of pain remission. Moreover, during the 4-week follow-up period after termination of treatment, the recurrence rate of pain in the ZY5301 groups was also low, with more than 90% of the participants evaluated able to maintain a clinical cure.

Figure 2. Effect of ZY5301 Tablet on Pelvic Pain (Full Analysis Set)

A Weekly VAS score over the treatment period

B Chronic pelvic pain remission rate

C Time to pain remission based on VAS score

VAS indicates visual analog scale.
In most patients with CPP, clinicians can also detect tenderness signs through gynecologic physical examinations. A clinical tenderness improvement was determined by assessing pelvic tenderness using the McCormack score. In our study, the significant decreases in the total McCormack score were observed in all 3 groups after 12 weeks of treatment, whereas the improvements in tenderness signs were better in the ZY3501 treatment groups than in the placebo group, with a statistically meaningful difference among groups.

The SF-12 is a multidimensional, universal measure of healthy living and is widely used in clinical outcome assessments. In our study, after 12 weeks of treatment, the SF-12 PCS results improved significantly for participants in both ZY3501 groups and the placebo group. However, significant improvements in the SF-12 MCS were only observed in the ZY3501 treatment groups, which may be explained by the quick and large reduction of pain with ZY3501 treatment.

Concerning safety, no significant differences were seen in TEAEs and TRAEs between the ZY3501 groups and the placebo group. No adverse drug reactions specific to ZY3501 tablets were observed. Our results showed that both ZY3501 300 mg/d and 600 mg/d had a good safety profile.

In addition to evaluating the preliminary efficacy and safety of ZY3501 tablets, this phase 2 clinical trial had 2 exploratory objectives, which were to determine the primary efficacy end point and the optimal treatment dosage for the phase 3 clinical trial. Considering that the pain remission rate may better reflect the clinical cure compared with change from baseline in VAS score, the pain remission rate at week 12 was chosen as the primary efficacy end point. Because the ZY3501 600 mg/d group had a better pain remission rate (53.5%) than the 300 mg/d group (43.3%), the higher dosage is recommended as the therapeutic dose for the phase 3 trial.

### Table 3. Adverse Events (AEs) in the Safety Population

<table>
<thead>
<tr>
<th>AE</th>
<th>No. of participants (%)</th>
<th>ZY3501 group 600 mg/d (n = 58)</th>
<th>300 mg/d (n = 60)</th>
<th>Placebo group (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td></td>
<td>21 (36.2)</td>
<td>23 (38.3)</td>
<td>17 (28.8)</td>
</tr>
<tr>
<td>Grade 1</td>
<td></td>
<td>10 (17.2)</td>
<td>17 (28.3)</td>
<td>10 (17.0)</td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td>10 (17.2)</td>
<td>4 (6.7)</td>
<td>7 (11.9)</td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td>1 (1.7)</td>
<td>2 (3.3)</td>
<td>0</td>
</tr>
<tr>
<td>SAEs</td>
<td></td>
<td>1 (1.7)</td>
<td>2 (3.3)</td>
<td>0</td>
</tr>
<tr>
<td>Any TEAE leading to drug discontinuation</td>
<td></td>
<td>1 (1.7)</td>
<td>0</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>TEAEs with incidence ≥3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td></td>
<td>2 (3.5)</td>
<td>5 (8.3)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
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<td>0</td>
<td>0</td>
<td>2 (3.4)</td>
</tr>
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<tr>
<td>Any TRAE</td>
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<td>2 (3.5)</td>
<td>1 (1.7)</td>
<td>3 (5.1)</td>
</tr>
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<td>2 (3.5)</td>
<td>1 (1.7)</td>
<td>2 (3.4)</td>
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<tr>
<td>Grade 2</td>
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<td>Grade 3</td>
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<td>Treatment-related SAEs</td>
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<tr>
<td>Any TRAE leading to drug discontinuation</td>
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<td>Specific TRAEs</td>
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<td>Abnormal T wave</td>
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Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
Limitations
This study has some limitations. First, the trial was conducted only in China. Second, the sample size was relatively small, and the effectiveness and safety of the study drug need to be evaluated in a larger patient population in the future. Third, because the study drug is the extract of A decumbens Thunb., pharmacokinetic characteristics of the ZY5301 tablets were not evaluated in our trial like other single compounds.

Conclusions
The results of this randomized clinical trial show that 12 weeks of ZY5301 tablet treatment led to a significant remission of CPP in patients with PID, with acceptable tolerability. Therefore, a dose of 600 mg/d is recommended for the phase 3 trial.

REFERENCES


SUPPLEMENT 1.
Trial Protocol

SUPPLEMENT 2.
eAppendix 1. Study Sites and Principal Investigators
eAppendix 2. Inclusion Criteria and Exclusion Criteria
eMethods.
eTable 1. Summary of VAS Scores From Baseline to Week 12 (FAS and PPS)
eTable 2. Short Form-12 (SF-12) and McCormack Scale (FAS)
eTable 3. Pairwise Comparisons Among the 3 Groups at Week 12 (FAS and PPS)

SUPPLEMENT 3.
Data Sharing Statement