SPONSOR: BOIRON

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NAME OF THE DRUG EVALUATED:
Actaea racemosa 9CH and Caulophyllum thalicthroides 9CH

TITLE OF THE STUDY:
RANDOMIZED DOUBLE-BLIND CLINICAL TRIAL TO MEASURE THE EFFICACY OF ACTAEA RACEMOSA (9CH) AND CAULOPHYLLUM THALICTROIDES (9CH) IN THE FIRST STAGE OF LABOR

INVESTIGATION CENTERS:
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This trial was approved by the AEMPS (spanish drug agency) on 24-09-2015, after receiving a favorable opinion from the CEIC (ethics committee of medicines) on 06-08-2015.

MAIN OBJECTIVE:
To determine the efficacy of treatment with Actaea racemosa (9CH) and Caulophyllum thalicthroids (9CH) from week 37 of gestation in the first stage of labor compared to placebo treatment. The first stage of labour is defined as the latent phase + active phase of dilation.

Design: Phase III, Multicentre, randomized, double-blind, placebo-controlled clinical trial with two parallel arms. Randomization has been stratified according to parity: primiparous or multiparous. 5 visits in total during the follow-up period (2 in primary care centre and 3 in Hospital).

Number of expected patients to be included: N= 114 (57 in each arm)

Inclusion criteria:
- Pregnant women between 32 and 33 weeks of gestation > 18 years old
- Single foetus in cephalic presentation at the time of recruitment

Main exclusion criteria:
-Previous caesarean, previous uterine surgery, chronic diseases, gestational pathology, etc..

Main withdrawal criteria:
-Gestational age ≥ 41 weeks, induction of labor (drugs, Hamilton or amniorresis), caesarean delivery, delivery complications, premature membrane rupture, etc…

Treatment:
Study patients were randomly assigned to study treatment (Actaea racemosa 9CH + Caulophyllum thalicthroides 9CH, globules) or control treatment (placebo).
• Weeks 37 and 38 of gestation: 5 globules / day
• Week 39 of gestation and until the beginning of the first stage of labor: 5 globules/ every 8 hours.

Development of the study:
The study started the 1th of March 2015 and ended the 24th of april 2019 (date of notification of the anticipated end of the trial).

Main Outcomes:
- The primary endpoint was the duration of the first stage of labor
- Main secondary outcomes were duration of first stage of labor , total duration of labor, evolution of Cervical Maturation(Modified Bishop's Test Score)

Safety parameters:
Blood safety variables: liver profile (Transaminases), kidney profile (creatinine and urea) and blood count.
Incidence and severity of adverse events occurring during the study.

Results of the study:
First patient was included on 01/03/2016.
A total of 157 patients have been included in this study, of which only 69 completed the trial to the end.
During the follow-up period, there have been 85 early dropouts from the study.
4 were before starting the treatment and randomized.
For the other 81 patients, early dropout was associated with "other causes", and not related with low efficacy, severe adverse event or major protocol deviation.
Majority of dropouts were associated with withdrawal criteria's previously established in the protocol, most of them premature membrane ruptures.
The high incidence of withdrawal (54 %) has led to have only 69 patients after 3 years since the start of the study, instead of the 114 initially calculated to achieve statistical significance.
On 08/07/2019, the study is declared as anticipated ending (AEMPS, CEIC).
As specified in the protocol for the safety assessment objective, all adverse events (AAs) were recorded throughout the follow-up visits, classified according to their intensity, severity, and relationship to treatment.
n= 77 patients were exposed to treatment group and n= 76 to placebo.
17 patients (22%) from treatment group has Adverse Events (AE) vs 21 (27.6 %) in group placebo.
During the follow up, 3 DSUR (Development Safety Update Report) have been submitted to local authorities. The last one covering the period from 01/03/2016 to 24/04/2019.
No Serious Adverse Reactions (SAR) have occurred during the clinical trial in the period covered by this last report.
During the period covered by this report, there have been no Adverse Events or Serious Adverse Events related to the investigational drug, nor have there been any serious and unexpected adverse reactions.

CONCLUSION
The phase III clinical trial to measure the efficacy and safety of Actaea racemosa (9CH) and Caulophyllum thalictroides (9CH) in the first stage of labor, has ended prematurely and therefore did not led to efficacy data.
Safety: no new data have been identified on safety of Actaea racemosa and Caulophyllum thalicthroides that modify the benefit-risk profile of the investigational medicinal products.