NCT02323646

Study ID: ZPV-201

Title: A Phase 2, Multi-Center, Parallel Design, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of 6 and 12 mg Proellex® (Telapristone Acetate) Administered Vaginally in the Treatment of Premenopausal Women with Confirmed Symptomatic Uterine Fibroids

Statistical Analysis Plan Amendment 1 Date: 06 April 2016

Repros Therapeutics Inc.
2408 Timberloch Place, B-7
The Woodlands, TX 77380

Statistical Analysis Plan

Protocol Number: ZPV-201

A Phase 2, Multi-Center, Parallel Design, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of 6 and 12 mg Proellex® (Telapristone Acetate) Administered Vaginally in the Treatment of Premenopausal Women with Confirmed Symptomatic Uterine Fibroids

Issue Date: June 20, 2016
Amendment I

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List of Abbreviations and Definitions

AE	Adverse event
Cavg	Average concentration
Cmax	Maximum concentration
CRF	Case report form
DHEA	Dehydroepiandrosterone
dL	Deciliter
ECG	Electrocardiogram
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	Gonadotrophin releasing hormone
g	Grams
hCG	Human chorionic gonadotrophin
ICH	International Conference on Harmonization
IGF-1	Insulin-like growth factor-1
IRB	Institutional Review Board
IND	Investigational new drug
IUD	Intra-uterine device
kg	Kilogram(s)
LD50	Median lethal dose
LH	Luteinizing hormone
LOCF	Last observation carried forward
LSC	Least Significant Change
m	Meters
MBL	Menstrual Blood Loss
mg	Milligram(s)
mL	Milliliter
ng	Nanograms
OC	Oral Contraceptive
ODI	Off-Drug Interval
PBAC	Pictorial Blood Loss Assessment Chart
PCOS	Polycystic Ovarian Syndrome
PK	Pharmacokinetic
RBC	Red blood cell
SAE	Serious adverse event
UFSQOL	Uterine Fibroid Symptom Quality of Life Survey
UFS-SSS	Uterine Fibroid Symptom Quality of Life Survey Symptom Severity Score (first 8 questions)
WBC	White blood cell

1. INTRODUCTION/BACKGROUND

This statistical analysis plan (SAP) describes the data analysis specifications for study ZPV-201, entitled "A Phase 2, Multi-Center, Parallel Design, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of 6 and 12 mg Proellex® (Telapristone Acetate) Administered Vaginally in the Treatment of Premenopausal Women with Confirmed Symptomatic Uterine Fibroids". The preparation of this version of the SAP adheres to Amendment 4 of the ZPV-201 protocol.

2. STUDY OBJECTIVES

The purpose of this study is to determine the safety and efficacy of two doses of Proellex compared to placebo in premenopausal women with symptomatic (menorrhagia) uterine fibroids confirmed by MRI.

3. STUDY DESIGN

3.1 OVERVIEW AND LENGTH OF STUDY

ZPV-201 is a phase 2 3-arm study with two 18-week dosing courses. The study will be conducted in 2 stages, with total study participation being approximately 18 months.

In the first stage, women will undergo a baseline assessment period with no treatment, until 15-20 days after the start of their second complete menstrual event. During this phase a pictorial blood loss assessment chart (PBAC) will be utilized as well as sanitary products collected from their first menstrual event, for alkaline hematin assay, to determine menstrual blood loss and confirm eligibility.

In the second stage, subjects will be randomized into one of 3 arms in a 1-1-1 fashion and receive two 18-week courses of treatment at their randomized dose level (6 mg, 12 mg, or placebo), separated by an off-drug interval (ODI). The start of the first 18-week course of treatment (Course 1) should commence 15-20 days after the start of their previous menses. Subjects should be instructed to continue vaginal dosing during their menses throughout the study and not to have sex or insert anything in the vagina for at least 1 hour after the capsule is inserted. Once dosing for Course 1 has stopped, subjects will be followed until menses return. The start of the second 18 week course of treatment (Course 2) will commence 15-20 days after the start of their menses following withdrawal of drug after Course 1 has been completed.

Efficacy will be assessed by: amenorrhea, PBAC scores, uterine fibroid symptoms-symptom severity score questionnaire (UFS-SSS), uterine fibroid volume, uterine volume, [redacted]

3.2 SAMPLE SIZE CALCULATION/JUSTIFICATION

Up to 50 female subjects, 15 per dose arm, meeting the inclusion/exclusion criteria will be randomized in a 1-1-1 fashion with the expectation that approximately 45 will be fully eligible for efficacy analyses. The primary endpoint is amenorrhea (no vaginal bleeding intensity > 1). A

[redacted]

4. ANALYSIS SETS

4.1 INTENT-TO-TREAT POPULATION

The Intent-to-Treat (ITT) population will consist of all patients who are randomized and who receive study drug.

4.2 SAFETY POPULATION

The Safety population will consist of all patients who are randomized, who receive study drug, and who have some post-baseline assessment of safety data.

5. ENDPOINTS

Efficacy endpoints will be:

- Percentage of subjects who become amenorrheic
- Percentage change in PBAC scores
- Percentage change in total and individual UFS-SSS scores
- Percentage change in size of uterine fibroids as assessed by MRI
- Percentage change in uterine volume as assessed by MRI

[redacted]

[redacted]

6. STATISTICAL METHODOLOGY AND ANALYSES

6.1 General Considerations

Standard statistical methods will be employed to analyze all data. It is anticipated that the following techniques may be used: t-test, ANOVA, chi-square test, Fisher's exact test, McNemar's/Bowker's test. Assumptions of normality will be tested using the Shapiro-Wilk test. If distributional assumptions are violated, non-parametric techniques, such as the Wilcoxon signed-rank test, Wilcoxon rank-sum test, and Kruskal-Wallis test, will be employed. Summaries for quantitative variables will include the sample size, mean, median, standard deviation, minimum, and maximum. Summaries for categorical variables will include the number and percent of patients for each outcome.

A last observation carried forward will be used to impute missing data for efficacy variables in the form of a "last observation on treatment".

Statistical significance will be declared if the two-sided p-value is ≤ 0.05.

Additional statistical analyses, other than those described in this SAP, may be performed if deemed appropriate.

6.2 Interim Analyses and Final Analyses

Two sets of analyses will be performed. The first analyses (efficacy endpoints only) will be performed after all subjects complete the first cycle of treatment, and to prevent unblinding, all clinical research and site staff will remain blinded at the subject-level. The second analyses (all endpoints) will be performed after all subjects are finished participating in the study.

6.3 Adjustment for Multiple Comparisons

No adjustments for multiple comparisons will be made in this study.

6.4 Extent of Exposure

The duration of exposure will be calculated for each subject. Summary statistics will be presented for each treatment group using the Intent-to-Treat population.

6.5 Subject Disposition

Subject disposition will be summarized in terms of the number of subjects who completed the study and discontinued early from the study. Disposition will be summarized for each treatment group using the Intent-to-Treat population.

6.6 Deviations

The total number of each deviation type will be summarized for the Intent-to-Treat population.

6.7 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized for the Intent-to-Treat population. Demographic and baseline data will be listed for all subjects to supplement summary results. Results will be presented for each treatment group.

6.8 EFFICACY ANALYSES

The efficacy analyses will be conducted using the Intent-to-Treat population, as defined in Section 4.1.

6.8.1 Amenorrhea

The proportion of subjects who become amenorrheic will be summarized for each treatment group. Treatment groups will be compared using a chi-square or Fisher's exact test, as appropriate.

[redacted]

A subject will be considered amenorrheic if they have no bleeding intensity score greater than 1 during a given interval.

The time to amenorrhea in each treatment course will be determined for each subject. This will be calculated as the difference in days between the last bleeding day during a treatment course and the start of treatment in that course. If a subject did not become amenorrheic by the time they reached their last 28 days on-drug during a treatment course then they will be censored. If a subject never experienced a bleeding day after starting treatment in a particular course then they will have their time to event set to 0 days for that course. Other variables may also be examined to determine if they affect time to amenorrhea.

6.8.2 PBAC

Total PBAC scores will be determined from daily PBAC entries grouped into the following 28 day intervals:

[redacted]

[redacted]

Total PBAC scores and percentage change from baseline in Total PBAC scores will be summarized for each treatment group. Pairwise comparisons between treatment groups will be performed using t-tests and Wilcoxon rank-sum tests, as appropriate. Statistical significance of the change from baseline within treatment groups will be determined using a paired t-test or Wilcoxon signed-rank test, as appropriate.

6.8.3 UFS-SSS

The individual and combined symptom severity scores and percentage change from baseline will be summarized at the end of course 1 treatment, course 2 treatment, and each follow-up visit. Pairwise comparisons between treatment groups will be performed using t-tests and Wilcoxon rank-sum tests, as appropriate. Statistical significance of the change from baseline within treatment groups will be determined using a paired t-test or Wilcoxon signed-rank test, as appropriate.

6.8.4 Uterine Fibroids

Uterine fibroid volume (by prolate ellipsoid method) will be determined by MRI. [redacted]

Total fibroid volume and percentage change in total fibroid volume will be summarized. Pairwise comparisons between groups will be performed using t-tests and Wilcoxon rank-sum tests, as appropriate. Statistical significance of the change from baseline within treatment groups will be determined using a paired t-test or Wilcoxon signed-rank test, as appropriate.

6.8.5 Uterine Volume

Uterine volume (assessed by MRI) and the percentage change in uterine volume will be summarized. Pairwise comparisons between groups will be performed using t-tests and Wilcoxon rank-sum tests, as appropriate. Statistical significance of the change from baseline within treatment groups will be determined using a paired t-test or Wilcoxon signed-rank test, as appropriate.

[redacted]

[redacted]

6.9 SAFETY ANALYSES

The safety analyses will be conducted using the Safety population, as defined in Section 4.2.

6.9.1 Adverse Events (AEs)

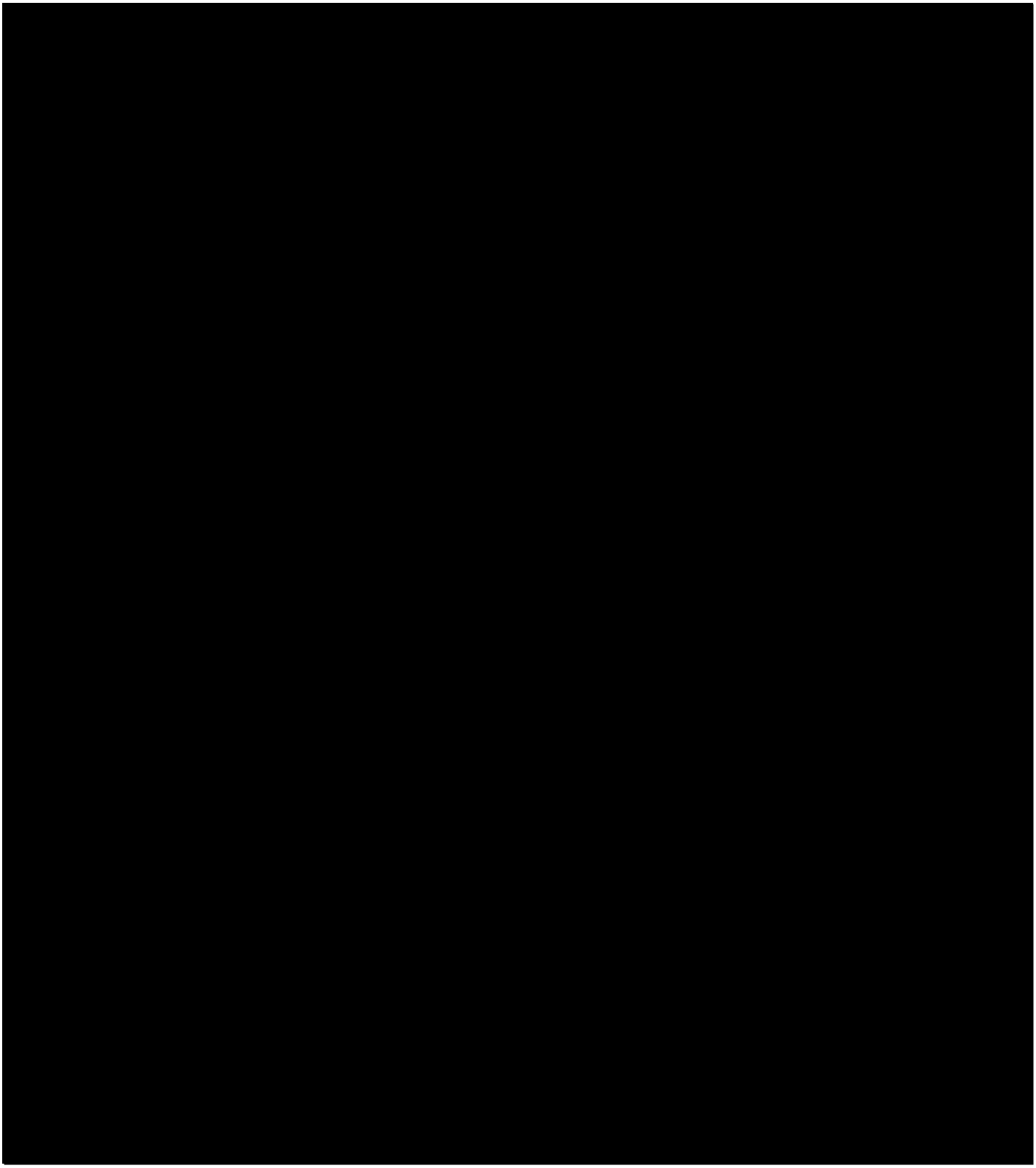
Treatment-emergent AEs (TEAEs) are defined as those AEs with an onset date and time equal to or after the start of study medication, or those events in which the onset date and time are before the start of study medication but worsened after the start of study medication. To be conservative, in the case of a missing onset time for an AE, an AE with a start date equal to or after the dosing date will be considered treatment-emergent. AE's with missing onset dates will also be considered treatment-emergent.

All TEAEs will be summarized by treatment group. The number of TEAEs as well as the number and percentage of subjects who experienced at least one TEAE will be summarized for each system organ class and each preferred term. The percentage will be based on the number of subjects in a particular treatment group included in the Safety population. Each subject will contribute at most one count per summarization category. TEAEs potentially related to study medication, serious TEAEs, and TEAEs leading to withdrawal will be summarized in a similar manner.

If a subject has more than one AE that codes to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than one AE within a system organ class category, the subject will be counted only once for that system organ class category.

TEAEs will also be summarized by maximum severity and by strongest relationship to treatment within each treatment group. Serious adverse events (SAEs) will be tabulated and listed in a

manner similar to TEAEs. A listing of all AE data will be provided to supplement the tabulated results.



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Statistical Analysis Plan

Protocol Number: ZPV-201

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Issue Date: April 6, 2016

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6.7 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized. A subject's age will be calculated as the number of years from the subject's date of birth to the date the Informed Consent document was signed, rounded down to the nearest integer:

Age = Integer ([Date Informed Consent Signed - Date of Birth] / 365.25)

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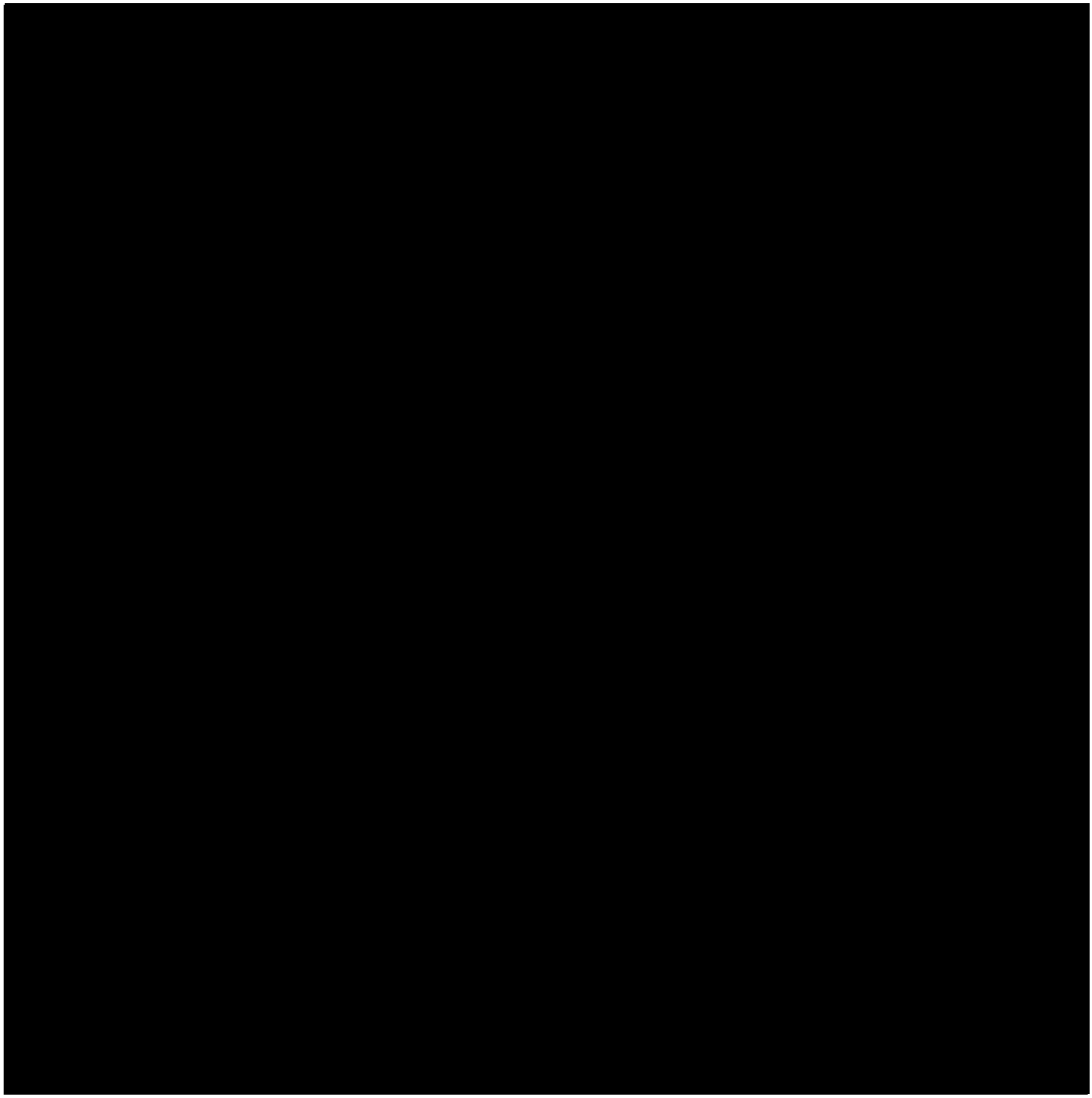

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