Appendix 1. Entry Criteria for Phase 3 Study Evaluating Levonorgestrel 52 mg Intrauterine Device for Heavy Menstrual Bleeding Treatment

Inclusion Criteria

1. Signed informed consent
2. Reports subjectively heavy menses for most menses when not using hormonal contraception or a copper IUD
3. Healthy females 18-50 years old, inclusive, at the time of enrollment
4. Able to read and write, as determined by study personnel
5. FSH value ≤30 mIU/mL at screening
6. Typical menstrual cycle length of 21-35 days with variation from cycle to cycle of typically 5 days or less
7. Has withdrawal bleeding in 2 of the 3 cycles during the Screening Phase with ≥ 80 mL per cycle as measured by the alkaline hematin method
8. Uterine sound depth of ≥5.5 cm
9. Willing to comply with study visit schedule and assessments, including menstrual product collection and diary completion requirements
10. Documented (i.e., printed report) Pap testing, regardless of participant's age, and any indicated evaluation/treatment that demonstrates no need for further evaluation during the course of study participation (i.e., within 10 months after consent)
11. Planning to reside within a reasonable driving distance of a research site (approximately 150 miles) for duration of study participation
12. Willing to use a medication other than a NSAID as first-line treatment for any pain condition during the duration of study participation
13. Willing to abstain from heterosexual intercourse or use acceptable contraception during the screening phase; acceptable contraception includes male or female permanent contraception, withdrawal (if has been using as current method prior to screening) or a barrier method
14. If previously pregnant, at least one subjectively heavy menses prior to screening

Exclusion Criteria

1. Currently pregnant
2. Planning to attempt to become pregnant during the screening and treatment phases (i.e., up to approximately 11 months after consent)
3. Currently lactating or not having a subjectively heavy menses since discontinuation of lactation prior to screening

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4. Clinical diagnosis of perimenopause (in the opinion of the investigator) based on one or more of the following: changes in menstrual regularity (e.g., shorter, longer, absent, irregular), hot flashes, sleeping disorder, or changes in mood (e.g., depression, nervous tension, and irritability) within 3 months prior to or during the screening period
5. Screening blood laboratory value outside of the normal range that, in the opinion of the investigator, requires treatment or further work-up (i.e., are considered clinically significant)
6. Has poor venous access or significant history of inability to have blood samples drawn
7. Body habitus or history of lower genital tract abnormalities or prior surgeries which may prohibit proper visualization of the cervix or not allow the uterus to be appropriately instrumented
8. History of bicornuate uterus or any other abnormality of the uterus resulting in distortion of the uterine cavity or cervical canal incompatible with insertion
9. Prior (documented within 6 months) or Baseline study ultrasound examination demonstrating:
    a. A congenital or acquired uterine anomaly that distorts the uterine cavity or cervical canal incompatible with insertion;
    b. Endometrial polyps (unless previously removed),
    c. Fibroids meeting any of the following criteria:
        i. Distort the uterine cavity or cervical canal incompatible with insertion;
        ii. Submucosal location;
        iii. Exceeding 2 cm in the greatest dimension for any individual fibroid;
        iv. More than three fibroids of at least 1.5 cm in greatest diameter
    d. Clear evidence of adenomyosis consisting of any of the following:
        i. Subendometrial cysts
        ii. Diffuse adenomyosis based on a heterogeneous myometrial echotexture consisting of:
            1) Hyperechoic findings (islands of endometrial glands);
            2) Hypoechoic findings (associated muscle hypertrophy);
            3) "Venetian blind" appearance due to subendometrial echogenic linear striations and acoustic shadowing where endometrial tissues cause a hyperplastic reaction
10. Recently diagnosed or clinically evident cervicitis or upper genital tract infection at the time of IUD insertion (unless successfully treated and considered clinically cured for at least 7 days prior to enrollment)

11. History of pelvic actinomycosis infection (i.e., received antibiotic treatment; criterion does not include solely a history of Pap test with actinomyces)
12. Postpartum or post-abortion endometritis unless symptoms resolved at least 4 weeks prior to screening
13. Chronic endometritis on endometrial biopsy at screening (an endometrial biopsy performed within 6 months of Visit 1 could be used if a report is available with a tissue diagnosis)
14. Has any of the following premalignant or malignant diseases:
    a. Malignant melanoma
    b. Acute malignancies affecting blood or leukemias
    c. Gestational trophoblastic disease (unless at least one year with undetectable beta-hCG)
    d. Known or suspected cervical, ovarian, vaginal or vulvar cancer
    e. Uterine cancer or evidence of uterine malignancy, endometrial intraepithelial neoplasia (EIN) or hyperplasia on an endometrial biopsy at screening (an endometrial biopsy performed within 6 months of Visit 1 could be used if a report is available with a tissue diagnosis)
    f. History of breast cancer, or suspicion of breast cancer until proven otherwise
15. Has any of the following medical conditions:
    a. Bleeding diathesis (inherited or acquired)
    b. History of von Willebrand's disease or other known coagulopathy
    c. Uncontrolled significant hypertension defined as a sitting systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 95 mm Hg at any screening or enrollment visit unless treated and controlled within two weeks of discovery
    d. Presence or history of venous thromboembolic diseases (deep vein thrombosis, pulmonary embolism), presence or history of arterial thromboembolic diseases (e.g., myocardial infarction, stroke)
    e. Uncontrolled thyroid disorder
    f. Sickle cell anemia
    g. Diabetes mellitus that is poorly controlled or with end-organ/vascular complications
    h. Hyperprolactinemia at screening
    i. Acute or severe liver disease or liver tumor
    j. Poorly controlled bipolar disorder, schizophrenia, psychosis, major depressive disorder or other major psychiatric disorder according the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-5)
    k. History of a positive HIV test or having a partner who is known to be HIV positive

l. Current or history of alcohol, illicit drug or prescription drug abuse within 12 months prior to screening

16. Use of antifibrinolytics, platelet aggregation inhibitors, anticoagulants or other similar medications that can increase or decrease bleeding within 30 days prior to or during screening (*EXCEPTION: NSAIDs can be used as second-line treatment for pain management*)
17. Use of intrauterine or implantable contraception, progestin-only pills, combined hormonal contraceptives or oral progestin therapy within 30 days before screening
18. Depomedroxyprogesterone acetate (DMPA) injection within the past 9 months prior to screening (this exclusionary time period can be shortened to 6 months if the participant has also had two spontaneous menstrual cycles [requires minimum of 3 heavy menses] that meet criteria for normal menstrual cycle pattern)
19. Use of non-contraceptive estrogen, progesterone, progestin, testosterone, androgen or other gonadotropins (e.g., hCG) within 30 days before screening
20. Prior total or partial endometrial ablation or resection
21. History of a uterine aspiration or curettage procedure for any indication (other than an office biopsy) within 4 weeks of screening
22. Known or suspected allergy to levonorgestrel or hypersensitivity to any component of the product
23. Use of an experimental medication or receipt of an experimental treatment for any condition within 30 days of screening
24. Study staff or a member of the immediate family of a study staff
25. Any condition or circumstance that, in the opinion of the Investigator, would constitute contraindications to participation in the study or would compromise ability to comply with the study protocol, such as any concurrent medical condition that is not stable and well-controlled, that is likely to worsen, or that may require recurrent hospitalizations during study participation

Appendix 2. Study-Specific Menstrual Products for Participant Use During a Phase-3 Study Evaluating the Levonorgestrel 52 mg Intrauterine Device for Heavy Menstrual Bleeding Treatment

- Tampax Regular Tampons with flushable applicator
- Tampax Super or Super Plus tampons with flushable applicator
- Kotex Regular Maxi Pads
- Kotex Super Long Maxi Pads
- Kotex Overnight Maxi Pads with Wings
- Carefree Body Shape Pantiliners with Actifresh, Extra Long

Appendix 3. Comparisons of Treatment Success (a) and Change in Blood Loss (b) Over 6 Cycles in Participants With a Body Mass Index ≤35 kg/m² and >35 kg/m² in a Phase 3 Study Evaluating the Levonorgestrel 52 mg Intrauterine Device for Heavy Menstrual Bleeding Treatment

a. Treatment Success

	Number*	Treatment success†	P-value‡
Body Mass Index (kg/m²)			
≤ 35	65	60 (92.3%, 95% CI 85.8-98.8%)	0.68
> 35	24	21 (87.5%, 95% CI 74.3-100.0%)	

b. Change in Bleeding Outcome

	Baseline§		Cycle 6		Median Decrease‖	P-value¶
	Number	Blood loss (mL)#	Number	Blood loss (mL)#		
Body Mass Index (kg/m²)						
≤ 35	60	136.6	60	3.8	97.4%	0.33
		(IQR 111.5-191.7)		(IQR 0.0-10.9)	(IQR 89.9-100%)	
> 35	21	171.2	21	2.5	99.0%	
		(IQR 111.7-192.9)		(IQR 0.0-7.5)	(IQR 94.9-100%)	

IQR: interquartile range

* Participants with any follow-up bleeding evaluations

† Menstrual blood loss during treatment <80 mL and >50% reduction from baseline during the last 28-day cycle of treatment (Cycle 3 or Cycle 6).

‡ Fisher exact test

§ Only including 81 participants with Cycle 6 outcome

‖ Baseline to Cycle 6 only for participants with Cycle 6 outcome

¶ Comparing median decrease from baseline to Cycle 6 only for participants with Cycle 6 outcome (Wilcoxon Rank-Sum Test)

median

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