Weekly Isotretinoin Therapy for the Treatment of Moderate Acne Vulgaris

NCT Number: NCT04594759

11/3/2020

PROTOCOL TITLE:

Weekly Isotretinoin Therapy for the Treatment of Moderate Acne Vulgaris

SHORT TITLE:

WIT Study

PRINCIPAL INVESTIGATOR:

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1. Objectives / Specific Aims

The objectives of the study are to:

- determine if once weekly dosed isotretinoin is effective for moderate acne vulgaris
- evaluate patient satisfaction with once weekly dosed isotretinoin for moderate acne vulgaris treatment
- identify any adverse effects associated with once weekly dosed isotretinoin for moderate acne vulgaris treatment

2.0 Background

In current Dermatology practice, options for moderate acne vulgaris remain limited. Moderate acne is clinically defined as acne that has not responded to at least three months of topical therapy and is not severe enough for initial treatment with a conventional course of isotretinoin (formerly known as Accutane). The mainstay of treatment for moderate acne remains long courses of oral antibiotics, mainly tetracyclines (doxycycline, minocycline) and occasionally trimethoprim-sulfamethoxazole. Males with moderate acne, in particular, are especially limited in their treatment options as they are not eligible for hormonal management (spironolactone, oral contraceptive pills) like their female counterparts. Additionally, even for those regardless of gender who may eventually qualify for a traditional isotretinoin course, many insurance companies first require failure to respond to at least three months of oral antibiotics. Nagler et. al found that the average antibiotic use for moderate to severe acne prior to receiving isotretinoin was 331 days, with 15.3% of patients prescribed antibiotics for three months or less, 88% for six months or more, and 46% for at least one year.[1] Despite the widespread use of oral antibiotics in acne, antibiotic resistance is considered a global threat per the CDC[2], and there have been calls to limit their use in acne because of concerns of bacterial resistance[3,4,5]. Because of this, there is a significant need for more research on alternative treatment options for moderate acne.

Once weekly isotretinoin dosing has the potential to significantly improve moderate acne with good patient satisfaction and safety profile; however, no study findings on this treatment option have been published to date. The efficacy of isotretinoin, an oral vitamin A derivative, for treatment of acne has been well established. The traditional treatment course for severe acne consists of once to twice daily dosing (0.5-1 mg/kg/day) for 4-7 months (or 150mg/kg total cumulative dose). Though efficacious, there are numerous reported side-effects due to achieving the cumulative dose rapidly by once to twice daily dosing, such as severe dry skin, lips, and eyes, as well as liver enzyme and lipid abnormalities. Because of this, there have been studies exploring alternative isotretinoin dosing regimens including microdose, lower daily dose regimens (0.15-0.4 mg/kg/day[6], 0.25-0.4 mg/kg/day[7], 0.3-0.4 mg/kg/day[8,9], in addition to 5 mg/day[10] and 0.15-0.28 mg/kg/day with additional of local application of 1% clindamycin gel every other day[11]) and daily dosing for 7-10 consecutive days (0.5-0.7 mg/kg/day) out of each month only.[7,12,13,14] All studies had favorable outcomes with alternative dosing, despite the lower total cumulative dose versus conventional dosing. Those who also analyzed adverse effect rates with alternative isotretinoin dosing found that these were either rarely observed or similar to conventional dosing.[6,8,9,10,12,14] In contrast, the potential adverse effects of oral antibiotics used for acne include photosensitivity and nausea/vomiting (doxycycline), drug-induced pigment deposition and drug-induced systemic lupus erythematosus

(minocycline), and angioedema and drug rashes including drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (trimethoprim-sulfamethoxazole). Interestingly, rates of acne recurrence between alternative isotretinoin dosing and conventional dosing were similar at follow-up,[6,7,9] despite a much older study from 1984 that found otherwise.[15] Additionally, cost of alternative isotretinoin dosing was lower than with conventional dosing,[8,9,13] and patient satisfaction was highest in the alternative dosing groups.[7,10]

For these reasons, we propose a study evaluating the efficacy of once weekly isotretinoin dosing (1-1.5 mg/kg/week) as a potential alternative to oral antibiotics for the treatment of patients with moderate acne. Secondary endpoints include patient satisfaction and adverse effects.

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2) Center for Disease Control (https://www.cdc.gov/drugresistance/biggest-threats.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fdrugresistance%2Fbiggest_threats.html)
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4) Bowe WP. Antibiotic resistance and acne: where we stand and what the future holds. J Drugs Dermatol. 2014;13(6): s66-s70.
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9) Kotori MG. Low-dose vitamin "A" tablets – treatment of acne vulgaris. Med Arch. 2015;69:28–30.
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11) Sardana K, Garg VK, Sehgal VN, et al. Efficacy of fixed low-dose isotretinoin (20 mg, alternate days) with topical clindamycin gel in moderately severe acne vulgaris. J Eur Acad Dermatol Venereol. 2009;23:556–60.
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13) Goulden V, Clark SM, McGeown C, Cunliffe WJ. Treatment of acne with intermittent isotretinoin. Br J Dermatol. 1997;137:106–8.
14) Kaymak Y, Ilter N. The effectiveness of intermittent isotretinoin treatment in mild or moderate acne. J Eur Acad Dermatol Venereol. 2006;20:1256–60
15) Strauss JS, Rapini RP, Shalita AR, et al. Isotretinoin therapy for acne: results of a multicenter dose-response study. J Am Acad Dermatol. 1984;10(3):490–496.

3.0 Intervention to be studied (if applicable)

Intervention: once weekly dosing of isotretinoin (1-1.5 mg/kg/week)

- FDA status: approved for moderate-severe acne vulgaris in ages 12 and older
- Please see Background for rationale on proposed dosing method
- Pharmacology: an oral retinoid (vitamin A derivative) that is thought to improve acne by decreasing sebaceous gland proliferation and function, though the exact mechanism is unknown. It is a lipophilic medication that is bound to plasma proteins; eating a high fat meal with the medication increases its bioavailability but not its half life (21 hours). It is metabolized into 4-oxo-retinoic acid, 4-oxo-isotretinoin, and tretinoin. It is excreted through the feces and urine.[16] Improvement of acne is due to drug accumulation. Drug serum concentration returns to physiologic level after about 2 weeks of taking the drug.[17]
- Safety: isotretinoin use is most commonly associated with xerosis and chelitis. It can more rarely be associated with hypersensitivity reactions, hypertriglyceridemia, hepatitis, agranulocytosis, musculoskeletal symptoms, pseudotumor cerebri, mood swings including depression, delayed wound healing, hearing impairment, and decreased night vision and corneal opacities. It can cause birth defects in women who become pregnant while taking the medication. There is a potential association with worsening of inflammatory bowel disease.[16] Because of this, all patients (men and women) who take isotretinoin must enroll in the IPLEDGE program prior to administration of medication.

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4.0 Study Endpoints (if applicable)

Primary endpoint: efficacy

Secondary endpoints: patient satisfaction, adverse effects

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria

- English-speaking patients 12 years and older with the diagnosis of moderate acne vulgaris

Exclusion Criteria

- Patients who are at baseline on long-term tetracycline antibiotics, long-term trimethoprim-sulfamethoxazole, or on spironolactone for any reason
- Patients who have taken isotretinoin in the past 6 months

- Patients with hypersensitivity to isotretinoin or to any of its components
- Females who are pregnant, likely to become pregnant, or will be breast-feeding during the study period
- Patients with a history of major depression, mania, or psychosis with an active episode during the past year including current psychotic symptoms and/or current suicidal ideation
- Adult patients with cognitive impairment
- Patients with baseline kidney or liver disease
- Patients with baseline hypertriglyceridemia
- Patients with history of or current pseudotumor cerebri
- Patients with any clinically significant unstable medical condition which could pose a risk to the safety of the patient
- Inability or unwillingness of subject or legal guardian/representative to give informed consent

6.0 Number of Subjects

Target enrollment is 50 participants to allow for attrition. Minimum expected enrollment is 30 participants.

7.0 Setting

Study site: outpatient dermatology clinics at MUSC.

8.0 Recruitment Methods

- Recruitment will occur during standard of care visits to the Dermatology Clinics including its virtual visits.
- The first person to inform eligible patients about the study will be a clinician directly involved in the eligible patient's care. The clinician will first determine if the patient may meet criteria (score of 3, moderate acne, on CASS clinical scale as described in more detail in section 10.0). If the patient expresses interest in the study, the clinician or study co-investigators will approach the patient without coercion and with the emphasis on the voluntary aspect of being enrolled in this study. He/she will also be told in a caring manner that no matter his/her decision, it will not affect his/her care. This discussion will take place either in-person during the patient's clinic appointment or over telephone within one business day of the appointment.
- If the discussion takes place in-person during the clinic appointment, the patient will be provided a printed recruitment pamphlet reiterating the information regarding the study (attachment A). Eligible patients who agree to participate will sign the study consent form. Weight will be obtained. A baseline photograph will be taken and uploaded into the patient's medical chart (Epic). Two baseline surveys (Dermatology Life Quality Index survey to assess patient satisfaction and a second survey regarding potential isotretinoin adverse effects) will be completed by the patient (attachments B and C, respectively). The patient's clinician will then counsel the patient on isotretinoin and IPLEDGE and enroll the patient in the IPLEDGE system following all prompts. The clinician will order baseline laboratory blood work (all patients) and

urinary pregnancy test (females). Once blood work has returned and is without any clinically significant abnormalities (see section 13.0), the weekly isotretinoin (at dose 1-1.5 mg/kg per week) will be prescribed by the clinician (for males). Females will need to wait an additional month to have a second negative pregnancy test before starting the medication per IPLEDGE standard of care. After a second negative pregnancy test at next monthly visit, the clinician can prescribe the weekly dosed isotretinoin.

- For any patient who is seeing his or her provider through a virtual visit and is interested in participating in the study, a study investigator can either counsel the potential participant in the provider's clinic (via virtual platform) or can call the patient to counsel over the phone. Consent can be obtained electronically (per REDCap guidelines). These patients will then have an in-person clinic visit scheduled with their provider to enroll in IPLEDGE so that the medication can be prescribed. Weight will be obtained. A baseline photograph will be taken and uploaded into the patient's medical chart (Epic). Two baseline surveys (Dermatology Life Quality Index survey to assess patient satisfaction and a second survey regarding potential isotretinoin adverse effects) will be completed by the patient (attachments B and C, respectively). The patient's clinician will then counsel the patient on isotretinoin and IPLEDGE and enroll the patient in the IPLEDGE system following all prompts. The clinician will order baseline laboratory blood work (all patients) and urinary pregnancy test (females). Once blood work has returned and is without any clinically significant abnormalities (see section 13.0), the weekly isotretinoin (at dose 1-1.5 mg/kg per week) will be prescribed by the clinician (for males). Females will need to wait an additional month to have a second negative pregnancy test before starting the medication per IPLEDGE standard of care. After a second negative pregnancy test at next monthly visit, the clinician can prescribe the weekly dosed isotretinoin.
- Additionally, if a study investigator is not available to counsel the patient at the time of the patient's clinic visit, and the clinician believes that the patient may qualify for the study, the clinician will send an Epic electronic health record message to the Study Coordinator (Dermatology research fellow) with the attached patient chart. The Study Coordinator will contact the patient by telephone within one business day. Over the phone, the study investigator will assess if the patient is eligible for the study and if he/she would like to participate. If so, an additional clinic visit (either in-person or virtual) will be set up with the patient's clinician to obtain a baseline photograph (alternatively the patient can also upload their own photos into MyChart), as well as to enroll the patient into IPLEDGE after counseling on the system and isotretinoin medication. Two baseline surveys (attachments B and C) and the study consent form (attachment E) will be sent electronically (per REDCap guidelines) for signature. These steps are outlined in directions for providers, a pamphlet that will be printed in each clinic site (attachment D). The signed consent form and two completed surveys can either be emailed back to the Study Coordinator for upload into the patient's medical chart (Epic) or photos of these can be taken by the patient for upload into their medical chart via MyChart (Epic). Once the patient is enrolled in both the study and IPLEDGE and is medically cleared to start isotretinoin, the clinician will prescribe the medication at the weekly study dose.

- No study-only procedures will be performed without first obtaining informed consent. Any standard of care procedures, tests, or visits can be completed at any time per clinical care team.
- The study will be posted on the new MUSC Dermatology Research Website. The study name, inclusion criteria and brief description of the study design will be posted. Patients interested in participating in the study will make an appointment with a member of the MUSC Dermatology Team as they must be followed by a dermatologist to receive their medication and have labs completed per standard of care IPLEDGE protocol.

9.0 Consent Process

- Study consent form is attached (attachment E). The method of obtaining consent including where this will take place and how this will be completed is detailed in above section 8.0. Counseling about the study and about the isotretinoin medication will take place prior to any signing of the study consent form. The participant will be asked to repeat back to the provider his or her understanding of the study and potential risks/benefits of the medication. The consent form for the study will be signed by the participant if the patient agrees to enroll in the study after counseling by a Study Coordinator. The participant will also enroll in IPLEDGE (isotretinoin monitoring system) with the help of the clinician where he or she will sign IPLEDGE consent forms.

- For participants who are not yet adults, parental permission will be obtained to enroll the participant with the participant's blessing. Assent will be obtained from all children during enrollment. If the participant turns eighteen during the study period, the participant will then provide written consent to continue the study; this will occur either in-person at a clinical visit or through electronic consent with a study investigator. Cognitively impaired adults are excluded from the study population.
- All participants will be reminded at each monthly follow-up visit that they can remove themselves from the study at any time.

10.0 Study Design / Methods

This will be an open-label, prospective, proof-of-concept study of patients with moderate inflammatory acne. The patients will be treated for at least 4 months.

- The initial acne assessment will be performed by dermatologists and dermatology residents using a validated, clinical grading system (Comprehensive Acne Severity Scale, CASS as below) with lesion counts (inflammatory and noninflammatory). Only moderate acne patients who are eligible for enrollment will be allowed to participate. Recruitment methods are outlined in above section 8.0. A baseline photo will be taken and placed in the patient's medical chart (Epic).

ASSESSMENT

ASSESSING SEVERITY OF ACNE

A new grading system named Comprehensive Acne Severity Scale – CASS (modification of an Investigator Global Assessment [IGA] of Acne Severity) is a validated tool which significantly correlates with the Leeds technique for face, chest and back.It is simpler to use in clinical practice.

Table 3: Comprehensive Acne Severity Scale (CASS)

GRADE*		DESCRIPTION
Clear	0	No lesions to barely noticeable ones. Very few scattered comedones and papules.
Almost clear	1	Hardly visible from 2.5 metre away. A few scattered comedones, few small papules and very few pustules.
Mild	2	Easily recognisable; less than half of the affected area is involved. Many comedones, papules and pustules.
Moderate	3	More than half of the affected area is involved. Numerous comedones, papules and pustules.
Severe	4	Entire area is involved. Covered with comedones, numerous pustules and papules, a few nodules and cyst.
Very severe	5	Highly inflammatory acne covering the affected area, with nodules and cyst present.

Inspection is done at a distance of 2.5 meters away for acne on face, chest and back.

- **Chest area defined as:** Anterior torso superiorly defined by suprasternal notch extending laterally to shoulders and inferiorly by a horizontal line defined by the xiphoid process.
- **Back area defined as:** (Is demarcated by the) superior aspects of the shoulders extending to the neck and inferiorly by the costal margins.

- The participants will be treated with once weekly isotretinoin at a dosage of 1-1.5mg/kg/week. Exact dosage will be determined by the provider.
- Efficacy will be determined by having one trained individual ("Photo Reviewer") grade patients' facial photographs to limit interrater reliability bias. This person will not be told what is being used as the study drug, and will not be told any details of the study, including that all participants are on the study drug, in order to limit observer bias (blinded). Every month, clinical photos will be submitted for each patient enrolled in the study. The participants will have these photos taken at monthly follow-up visits (monthly follow-up visits are standard of care per requirements of IPLEDGE, the medication monitoring system for isotretinoin). For in-person visits, these monthly photos will be taken by the provider or staff in clinic and directly uploaded to the Epic electronic medical record. For any virtual clinic visits (given the COVID-19 pandemic), the monthly photos will be submitted into MyChart by the patient.
- The Study Coordinator (Dermatology research fellow), who per the study consent form has permission to access participants' medical records for the purpose of the study, will follow each patient through Epic electronic medical record to confirm that photos are submitted in a timely manner.
- A separately trained individual ("Data Retriever"), who per the study consent form has permission to access participants' medical records for the purpose of the study, will submit any uploaded photos (baseline and at the end of each

month) from Epic to the Photo Reviewer by secure, encrypted email, labeling only with participant number and date of photo. This ensures that the Photo Reviewer is always reviewing only individual photos and will not ever enter the patient's medical chart to further limit bias.

- Photo Reviewer will receive photos and document a monthly CASS grade for each participant (in encrypted Excel only accessible by study team members, using study participant numbers without patient identifiers, attachment F). Baseline photos will all be a grade 3 (moderate) based on study inclusion criteria. "Improvement" is defined as decrease in grade from a 3 (moderate) to either a 2 (mild), 1 (almost clear), or 0 (clear). "Failure" is defined as showing no improvement (remaining a grade 3), increasing grade of 4 (severe) or 5 (very severe), or requiring additional oral treatment (for example, worsening acne requiring conventional dose isotretinoin). Treatment success can then be calculated as the percentage of participants with improvement out of the total number of participants at the end of four months, in addition to treatment success after each month of treatment.
- Any participants who take any oral tetracycline antibiotics or trimethoprim-sulfamethoxazole during the study period (for a reason besides acne) will be removed from the study in order to prevent any confounding. Patients requiring these medications for acne after the study period has begun will remain included in the study and will be listed as intervention "failure" as above. Participants will be allowed to continue use of topical acne cleansers and treatments during the study as per standard of care.
- Photo Reviewer will be a blinded medical student because all of the dermatology residents will be participating in the clinical care of study participants. The Photo Reviewer will be trained by the Primary Investigator (Dermatology Resident) and Study Coordinator (Dermatology Research Fellow) on how to use the objective CASS grading system.
- Data Retriever will be a Dermatology resident who will be trained by the Primary Investigator (Dermatology Resident) and Study Coordinator (Dermatology Research Fellow).
- All participants, regardless of whether they show "improvement" or "failure," will be followed for up to four months after the study period to assess for recurrence of acne. During this period, any further treatment decisions will be made by the patient and his or her clinician. Any participants who choose to continue once weekly isotretinoin will be asked to upload clinical photos and patient satisfaction surveys monthly through MyChart. Other participants who discontinue the isotretinoin will be asked about their follow-up acne treatment.

To determine patient adverse effects (secondary endpoint), we will monitor for side-effects of the interventional medication.

- Per standard of care, patients will be enrolled in IPLEDGE, requiring extensive counseling before starting the isotretinoin medication, monthly follow-up visits for males and females, and monthly urine pregnancy tests for females.
- Each patient will fill out a survey at baseline (attachment C) and at each monthly visit (attachment G) inquiring about potential side-effects of isotretinoin (with severity) including dry skin, dry mucous membranes (lips,

eyes), GI upset, bone or muscle pain, night vision abnormalities, mood swings/depression, headaches, delayed wound healing. If the follow-up visit between the patient and his or her clinician is virtual, the attached surveys will be sent in an encrypted email for completion by the participant. Photos of each completed survey will be uploaded into the patient's chart either at their clinic visit or by the patient via MyChart (virtual visit).

- Per standard of care, laboratory blood work (CBC, CMP, lipid panel) will be obtained prior to starting the medication and will be repeated two months into the study period (after two clinical follow-up visits, also per standard of care and confirmed by PRA), or more frequently if clinically indicated. The results will be reviewed from the medical record.
- Pregnancy test data will be collected from the medical record as these will be performed as part of the clinical care of the patient. Female participant's individual providers will order pregnancy tests, which per standard of care are typically collected at baseline x 2 (one month apart), every month while on the medication, and at least one month after stopping the medication. If patients have any significant laboratory abnormalities that could be related to the medication, the medication will be discontinued.
- The Study Coordinator (Dermatology research fellow) will follow each patient through Epic electronic medical record to confirm that laboratory work and surveys are completed in a timely manner.
- Data Retriever will follow each participant's laboratory blood work and any abnormalities will be entered into the encrypted Excel sheet; this individual will also enter all survey responses into the same encrypted Excel sheet (attachment F).

To determine patient satisfaction (secondary endpoint), the Dermatology Life Quality Index (https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/dermatology-life-quality-index) will be administered at baseline before receiving any medication and at each monthly follow-up visit. The DLQI is the most frequently used validated, patient-reported outcome measure in dermatology trials (attachment B). License for use of survey has been obtained (attachment H).

- Data Retriever will follow each participant's surveys and enter information into the same encrypted Excel sheet as noted above.

11.0 Specimen Collection and Banking (if applicable)

- Urinary pregnancy tests (obtained per standard of care per IPLEDGE requirements and per the clinical care team) may be collected at each participant's clinic visits in the MUSC outpatient dermatology clinic. For virtual follow-up visits, per current standard of care by IPLEDGE during COVID-19 pandemic, females can also take a home pregnancy test and label with name, date, and time and submit a photo of the test through MyChart (Epic). Pregnancy test results will be obtained from the medical record. Laboratory blood work will be drawn through either the MUSC lab or through LabCorp so that results will be automatically uploaded into the patient's Epic medical chart. No specimens will be collected or kept by investigators.

12.0 Data Management

- Participant clinical photos, signed consent form, and photos or scans of their completed surveys will be uploaded into the Media tab of Epic electronic health record either in clinic or by the patient through MyChart. Laboratory result information will result in the patient's Epic medical chart. This will keep this information secure and protected. Study team members will have permission to access study participants' medical records for the purpose of retrieving information for the study, as listed in the study consent form.
- Data Retriever will securely email ("send secure") the participant photos (deidentified) to the Photo Reviewer to score. This will occur over MUSC email only.
- Storing of synthesized study information (participant follow-up dates, scoring of clinical photos, list of any participant lab abnormalities, participant survey answers) will be entered in an encrypted Excel sheet, labeled only with participant number and without patient identifiers (attachment F). Only investigators directly involved with the study will have access to this encrypted Excel sheet.
- Paper consent forms will be stored in a locked office (Rutledge Tower, dermatology office floor 10). Electronic consent forms will be stored on a MUSC desktop computer that is secured by username and password. Photos of all consent forms will be taken for upload into patient's Media tab in their medical chart.
- Since this is a proof-of-concept study, there will not be any statistical analysis. Observations will be reported.
- Data will not leave MUSC.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

- Data Retriever (as above), the Principal Investigator, and the Study Coordinator will serve as a data monitoring committee. At the end of each month, Data Retriever will review each participant's laboratory blood work results and surveys and input the information into the encrypted Excel sheet. This Excel sheet will be reviewed by the rest of the data monitoring committee. The clinicians that see each participant will also review laboratory blood work as it is completed and are instructed to notify the investigators with any significant abnormalities as they arise. Any pertinent abnormalities (elevated liver enzymes, elevated triglycerides) will be discussed with the patient by their individual providers and the decision to continue or discontinue isotretinoin will be a joint patient-provider decision made at that visit based on clinical judgement. Additionally, any clinically significant baseline laboratory abnormalities will exclude the patient from enrolling in the study. If the patient's liver enzymes or triglycerides increase to > 3 times the upper limit of normal during the study period, the medication will be stopped.

14.0 Withdrawal of Subjects (if applicable)

- Study investigators may withdraw a participant from the study at any time at their discretion. Circumstances can include when a participant's safety may be compromised such as when a participant is experiencing adverse events requiring discontinuation of the drug, if the study is stopped in relation to risk to participants, or when the participant is non-compliant with the medication regimen.
- A study investigator will inform the participant that he or she has been withdrawn from participation and the reasons therefore.

- At any time, a participant can withdraw from participation in some or all components of the study.
    - When the participant withdraws, the participant will no longer receive isotretinoin at the experimental regimen.
    - The participant's medical record or other confidential records will not be accessed by the investigator.
    - The data collected to the point of withdrawal will remain part of the study records.
- At a minimum, documentation of the participant's withdrawal will include the date, rationale, and which component the participant is withdrawing.
- The Primary Investigator will inform the IRB of the number of participants who withdrew and the reason for withdrawal.

15.0 Risks to Subjects

- There is a risk of a loss of confidentiality of personal information as a result of participation in this study which will be mitigated at all costs by the study team members.
- There is a risk to embryos of females who become pregnant while on isotretinoin. The participant will be educated extensively on these risks and enrolled in the IPLEDGE program which per standard of care requires two forms of birth control for females of child-bearing potential while on isotretinoin, pregnancy tests at baseline, pregnancy tests each month while on the medication, and again one month after stopping the medication.
- Risks to participants include those that are present when taking isotretinoin at the conventional, higher dose. Potential side-effects of isotretinoin include dry skin, dry mucous membranes (lips, eyes), GI upset, bone or muscle pain, night vision abnormalities, mood swings/depression, headaches, delayed wound healing, and laboratory abnormalities (namely hypertriglyceridemia, elevated liver enzymes). Frequent monitoring by the patient's clinician and monthly monitoring by the data monitoring committee will take place to minimize risks to participants (detailed in section 13.0). These participants will be taking isotretinoin only once weekly, at a dose equivalent of what patients usually take once daily; study dose is 1/7 of the usual, weekly total dose. Because of this, we have reason to believe that risks will be either the same or less than risks while on conventional dose isotretinoin.
- There is a risk of emotional distress when filling out the monthly surveys. If the participant admits to feeling depressed thoughts, the participant will be given the appropriate resources and a psychiatric referral can be placed if the patient wishes. If the patient admits to suicidal or homicidal ideation, inpatient psychiatry will be consulted.

16.0 Potential Benefits to Subjects or Others

- Potential benefit of intervention is improvement in participants' moderate acne vulgaris. There is benefit of minimal dosing, as well as avoidance of long-term antibiotics (and of antibiotic resistance).

- An additional potential benefit is contributing to furthering medical knowledge regarding isotretinoin and moderate acne. If participants show a benefit to this alternative isotretinoin dosing, further larger and randomized studies can be completed.
- Risks are reasonable in relation to the anticipated benefit to participants. Risks to participants include those that are present when taking isotretinoin at the conventional, higher dose (detailed in section 15.0). These participants will be taking isotretinoin only once weekly, at a dose equivalent of what patients usually take once daily; study dose is 1/7 of the usual, weekly total dose. Because of this, we have reason to believe that risks will be either the same or less than risks while on conventional dose isotretinoin.

17.0 Sharing of Results with Subjects

- Because this is an open-label study, all participants will know what medication they are taking and at what dose.
- Information such as standard of care lab results will be returned to the patient once of the results are available. Abnormal results will be followed up by the patient's clinician and data monitoring committee.
- Results regarding the participants and overall response to the medication will be withheld during the study until the results are analyzed.

18.0 Drugs or Devices (if applicable)

- Isotretinoin (study drug) will be prescribed to each participant through Epic electronic medical record. The medication will be paid by each patient's insurance or by self-pay (per MUSC Rutledge Tower Pharmacy, this dosing should be covered by most insurance plans and is otherwise $10.36 for a 40 mg isotretinoin pill). The participant will directly pick up the medication each month from the pharmacy and will store the medication at home in a safe, shaded, secure place. The investigators and study team will not handle or store any study drug.

References

All references are noted and listed by number under their respective sections.
All attachments are noted and listed by letter within the text and highlighted in yellow.