Participating in Clinical Research

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Clinical Care vs. Research Studies

**Clinical Care = regular medical care based on patient needs**
- Benefits an individual patient
- Uses products and procedures accepted as safe and effective
- Evaluation results are provided to patient and not released to others without written authorization
- Overseen by state boards of medical practice, informed consent, professional/legal standards
- Funded by patient insurance

**Research Studies = discovering answers to a SPECIFIC question(s)**
- Often designed to benefit future patients
- Tests products/procedures of unproven benefit to study participant
- Evaluation results may, or may NOT, be shared with study participant. Results of the entire study may be published in a medical journal
- Data is viewed by multiple individuals on the study team
- Overseen by FDA, Institutional IRB, informed consent, professional/legal standards
- Funded by private companies and government agencies

Adapted from: https://www.fda.gov/ForPatients/ClinicalTrials/ClinicalvsMedical/default.htm
Institutional Review Board (IRB)

Board, group or committee designated by an institution to protect the rights and welfare of human study participants

- Review research studies before they begin
- Approve the start of research studies
- Periodically review and evaluate research studies while they are ongoing

IRBs can be at a large institution or centralized
Examples of Types of Research Studies

- **Registries / Natural History**
  - What happens over a period of time to someone with condition X?
  - What happens to people if given treatment X?
  - Identify associations, don’t necessarily prove cause and effect

- **Research Studies**
  - I want to learn more about ???
  - Conducted to find answers to specific questions
  - Numerous types of study designs and methods

- **Clinical Trial / Pharmaceutical Intervention**
  - Does a drug work to treat X of condition X?
  - Evaluate the effectiveness of treatment measures
Registries and Natural History Studies

- **Generally an OBSERVATIONAL study**
  - “What happens over time to someone with condition X?”
  - “What happens to someone with condition X if they take Drug X?”

- **Generally consists of a chart review**
  - Data collected is derived from evaluations performed as part of routine care
  - Data is generally obtained from participant’s chart
  - Study participants may be asked to fill out questionnaires
Investigator-Initiated Studies

Investigator-Initiated Studies are studies by an individual researcher, generally not a company

- Often funded by government grants or private donors
- Usually smaller in scale than clinical trials for pharmaceuticals
- Participants may NOT receive the results of study evaluations
  - Participation may be “for the greater good”
  - Data may become available as part of a large publication at a later date
Clinical Trials or Pharmaceutical Studies
(aka Interventional Studies)

- Studies generally conducted by a pharmaceutical company
  - Demonstrate the safety and efficacy of a new drug
  - Demonstrate new use for a previously approved drug
- Funded by sponsoring pharmaceutical company, known as "sponsor"
- Oversight by FDA and local institution (IRB)
  - Reviews earlier research/animal data and sponsor’s plan for clinical trial
  - Reviews data at set intervals during clinical trial
  - Ensures participant safety
Informed Consent

It’s more than signing a piece of paper!!

- **WHY**: To ensure participants have learned the key facts about the research study and to confirm **VOLUNTARY** participation
- **WHEN**: Must be obtained **BEFORE** initiating any screening or study procedures
- **WHERE**: Generally in-person with a study representative
  - Location should be free of distractions
- **HOW**: Generally reviewed with a study coordinator
  - Interpreters should be made available, if needed
  - Participants should receive a copy
Informed Consent

**WHAT**: Signed summary document with an overview of the study including:

- Procedures/evaluations with descriptions and frequency
- Study Duration/Timeline
- Risks and Benefits of study participation
- Alternatives to participation
- Option to discontinue study participation
- Research-related injuries including treatment and/or compensation
- Contact phone numbers for research team and someone independent of research team
Informed Assent

Signed, written agreement by a minor to participate in research

- Designed to ensure willing, informed participation by minors
- “Failure to object” is not considered assent

Age of Assent is variable, but may be as young as 7

- Age of Assent varies by institution and relies on the expertise of study investigators to determine capacity to provide assent:
  - Age of child
  - Maturity
  - Psychological State

- Consent from both, or sometimes one, parent/guardian is still required in the majority of research studies

Clinical Trial Phases

***These definitions can be blurred or combined in rare conditions***

- Phase I – Safety and correct dose
- Phase II – Efficacy and side effects
- Phase III – Efficacy and adverse
- Phase IV – Safety and efficacy
- Compassionate Use

https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm
http://www.phrma.org/advocacy/research-development/clinical-trials
Phase I

Purpose: Safety and Dosage

- What is a safe dose?
- How does drug interact with, or affect, the human body?
- Usually conducted with a small number of healthy/unaltered individuals
- Phase I is short duration = months

http://www.phrma.org/advocacy/research-developmentclinical-trials
**Phase II**

**Purpose:** Efficacy and side effects

- Does this drug do what it’s intended to do?
- Are there any side effects on the dose determined in Phase I?
- Usually conducted with a larger number of affected individuals
- Phase II is longer duration = months to years

[http://www.phrma.org/advocacy/research-development/clinical-trials](http://www.phrma.org/advocacy/research-development/clinical-trials)
Phase III

Purpose: Efficacy and adverse reactions/events

- Does the drug work and is it of benefit?
- Collects safety and side effect data, monitors any side effects
  - Adverse reaction/Event (AE) = side effect
  - Compare to commonly used treatments
- Large groups of participants
  - 100s - 1000s
- One to many years in duration
- Submission to FDA for approval after analysis of Phase III data

http://www.phrma.org/advocacy/research-development/clinical-trials
Phase IV

Purpose: Safety and efficacy

- Occurs **AFTER** drug has received FDA approval (aka post-marketing)
- Data collection to monitor any side effects long term
- Several thousand affected volunteers taking the drug

http://www.phrma.org/advocacy/research-development/clinical-trials
Compassionate Use
(aka Expanded Access)

- Use of a drug **BEFORE** FDA approval and outside of a clinical trial

- Application process to the FDA to grant expanded access
  - Patient and physician are willing to participate
  - No other available treatment options
  - Risk of using drug is not greater than the risk of the condition
    - Benefits outweigh risks
  - Use will not interfere with the clinical trial
  - Patient unable to receive treatment under another clinical trial
  - Treatment plan must be created and approved by FDA
ClinicalTrials.gov

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

Explore 259,961 research studies in all 50 states and in 201 countries.

ClinicalTrials.gov is a resource provided by the U.S. National Library of Medicine.

IMPORTANT: Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

Before participating in a study, talk to your health care provider and learn about the risks and potential benefits.

Search

Condition / Disease: e.g. breast cancer
Other Terms: e.g., NCT number, drug name, investigator name
Country: [ ]

Find a study to participate in  Search all studies

Advanced Search

Patients and Families
Search for actively recruiting studies that you may be able to participate in or learn about new treatments that are being considered.
Learn more

Researchers
Search the database to stay up to date on developments in your field, find collaborators, and identify unmet needs.
Learn more

Study Record Managers
Learn about registering studies and about submitting their results after study completion.
Learn more
<table>
<thead>
<tr>
<th>Row</th>
<th>Saved</th>
<th>Status</th>
<th>Study Title</th>
<th>Conditions</th>
<th>Interventions</th>
<th>Locations</th>
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<tr>
<td>1</td>
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<td>Active, not recruiting</td>
<td>A Natural History Study of Fibrodysplasia Ossificans Progressiva (FOP)</td>
<td>Fibrodysplasia Ossificans Progressiva</td>
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<td>Drug: Palovarvane</td>
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<td></td>
<td>Drug: REGN2477</td>
<td>Hospital Necker-Enfants Maladies, Department of Genetics Paris France</td>
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<td></td>
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<td></td>
<td>Drug: Matching placebo</td>
<td>The Royal National Orthopaedic Hospital, Brockley Hill Stanmore, Middlesex United Kingdom</td>
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<td>Recruiting</td>
<td>A Study to Examine the Safety, Tolerability and Effects on Abnormal Bone Formation of REGN2477 in Patients With Fibrodysplasia Ossificans Progressiva</td>
<td>Fibrodysplasia Ossificans Progressiva</td>
<td>Drug: REGN2477</td>
<td>Mayo Clinic Rochester, Minnesota United States</td>
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</table>
A Study to Examine the Safety, Tolerability and Effects on Abnormal Bone Formation of REGN2477 in Patients With Fibrodysplasia Ossificans Progressiva (LUMINA-1)

This study is currently recruiting participants.
See ▶ Contacts and Locations
Verified November 2017 by Regeneron Pharmaceuticals
Sponsor:
Regeneron Pharmaceuticals

Information provided by (Responsible Party):
Regeneron Pharmaceuticals

Purpose

This is a two period study design consisting of a 6-month, randomized, double-blind placebo-controlled treatment period 1) followed by a 6-month, open-label treatment period 2).

Primary safety objective of the study is to assess the safety and tolerability of REGN2477 in male and female patients with fibrodysplasia ossificans progressiva (FOP).

Primary efficacy objective of the study is to assess the effect of REGN2477 versus placebo on the change from baseline in heterotopic ossification (HO) in patients with FOP, as determined by 18F-NaF uptake in HO lesions by positron emission tomography (PET) and in total volume of HO lesions by computed tomography.

Secondary objectives are:
• To assess the effect of REGN2477 versus placebo on the change from baseline in HO, as determined by the number of new HO lesions identified by 18F-NaF PET or by CT
• To compare the effect of REGN2477 versus placebo on the change from baseline in 18F-NaF standardized uptake value maximum (SUVmax) of individual active HO (also by PET)
• To compare the effect of REGN2477 versus placebo on pain due to HO, as measured by the area under the curve (AUC) for pain based on daily numeric rating scale (NRS) scores
• To assess the effect of REGN2477 versus placebo on the change from baseline in biochemical markers of bone formation
• To characterize the concentrations of total activin A at baseline and over time following the first dose of study drug
**Phase II = Safety and Efficacy, is it safe and does it work??**

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Phase 2</th>
</tr>
</thead>
</table>

**Descriptive Information**

**Brief Title**
A Study to Examine the Safety, Tolerability and Effects on Abnormal Bone Formation of REGN2477 in Patients With Fibroblastosis Ossificans Progressiva.

**Official Title**
A Randomized, Placebo-controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Effects on Heterotopic Bone Formation of REGN2477 in Patients With Fibroblastosis Ossificans Progressiva.

**Study Type**
Interventional

**Condition**
Fibroblastosis Ossificans Progressiva

**Intervention**
- **Drug: REGN2477**
  - Pharmaceutical form: Powder for solution for injection/infusion; Route of administration: Intravenous (IV); Administered during treatment periods 1 and 2.
- **Drug: Matching placebo**
  - Pharmaceutical form: Powder for solution for injection/infusion; Route of administration: Intravenous (IV); Administered during treatment period 1 only.

**Study Arms**
- Experimental: REGN2477
  - Intervention: Drug: REGN2477
- Experimental: Placebo
  - Intervention: Drug: Matching placebo

**Publications**
Not Provided
Double-blind placebo controlled followed by Open Label – huh?

- **Double-blind** = study participant nor investigator (study doctor) know if drug is being given
- **Placebo controlled** = some study participants don’t receive drug
  - ”Sugar pill”
- **Randomized** = No control over who receives drug or placebo
  - Often the groups are equally divided, but not always
- **Open-label** = Everyone receives drug and everyone knows it

“This is a two period study design consisting of a 6-month, randomized, double-blind placebo-controlled treatment (period 1) followed by a 6-month, open-label treatment (period 2).”
### Inclusion and Exclusion Criteria

**Inclusion Criteria:**
- 40 total participants in BOTH United States and United Kingdom
- Expected completion of data analysis, then submit for approval
- All participants should be finished with all evaluations

### Key Inclusion Criteria:
1. Men and women 18 to 60 years of age at screening.
2. Clinical diagnosis of FOP based on findings of congenital malformation of the great toe, episodic soft tissue swelling, and/or progressive heterotopic ossification.
3. Confirmation of classic FOP diagnosis with documentation of the ACVR1P208H mutation.
4. FOP disease activity within 1 year of screening visit. FOP disease activity is defined as pain, swelling, stiffness, and other signs and symptoms associated with FOP flare-ups, or worsening of joint function, or radiographic progression of heterotopic ossifications increase in site or number of HO lesions with/without being associated with flare-up episodes.
5. Willing and able to undergo PET and CT Imaging procedures and other procedures as defined in this study.

### Key Exclusion Criteria:
1. Significant concomitant illness or history of significant illness such as, but not limited to, cancer, renal, hematologic, neurologic, psychiatric, endocrine, metabolic or lymphoma disease, that in the opinion of the study investigator might confound the results of the study or pose additional risk to the patient by their participation in the study.
2. Use of bisphosphonate within 1 year of screening.
3. Concurrent participation in another interventional clinical study, or a non-interventional study with radiographic measures or invasive procedures (e.g., collection of blood or tissue samples). Participation in the FOP Connect Registry or other studies in which patients complete study questionnaires are allowed.
4. Pregnant or breastfeeding women.
5. Male and women of childbearing potential patients who are unwilling to practice highly effective contraception.

### Additional Information:
- **Sex/Gender:** Both
- **Ages:** 18 Years to 60 Years (Adult)
- **Accepts Healthy Volunteers:** No
- **Contact:**
  - Clinical Trials Administrator: 844-734-6643
  - clinicastrials@regeneron.com
- **Listed Location Countries:**
  - United Kingdom, United States
Study Protocols

- SPECIFIC study plan to answer SPECIFIC questions
- Study questions are measured by ENDPOINTS or OUTCOME MEASURES
  - A measurable objective to determine if the intervention worked
  - Study sponsors or researchers determine the endpoints

<table>
<thead>
<tr>
<th>Estimated Primary Completion Data</th>
<th>June 12, 2019 (First data collection date for primary outcome measure)</th>
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</thead>
<tbody>
<tr>
<td>Current Primary Outcome Measures</td>
<td>• Incidence and severity of treatment-emergent adverse events (TEAEs) through the end of the Treatment Period 1 at week 26 [Time Frame: Baseline to week 26]</td>
</tr>
<tr>
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<td>• Time-weighted average (standardized area under the curve [AUC]) percent change from baseline in total lesion activity by 18F-NaF PET over 20 weeks [Time Frame: Baseline to week 20]</td>
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<tr>
<td></td>
<td>• Percent change from baseline in the total volume of HO lesions as assessed by CT at week 28 [Time Frame: Baseline to week 28]</td>
</tr>
<tr>
<td>Original Primary Outcome Measures</td>
<td>Same as current</td>
</tr>
<tr>
<td>Change History</td>
<td>Complete list of historical versions of study NCT03188668 on ClinicalTrials.gov Archive Site</td>
</tr>
<tr>
<td>Current Secondary Outcome Measures</td>
<td>• Percent change from baseline in 18F-NaF SUVmax of individual active HO site(s) by PET at week 8 [Time Frame: Baseline to week 8]</td>
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<td>• Change from baseline in number of HO lesions detectable by CT at week 28 [Time Frame: Baseline to week 28]</td>
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<td></td>
<td>• Time-weighted average (standardized AUC) change from baseline in daily pain due to FOR as measured using the daily NRQ over 26 weeks [Time Frame: Baseline to week 26]</td>
</tr>
<tr>
<td></td>
<td>• Change from baseline in the volume of individual HO lesions as assessed by CT at week 28 [Time Frame: Baseline to week 28]</td>
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<tr>
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<td>• Incidence and severity of TEAEs through the end of study [Time Frame: Baseline to week 76]</td>
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<td>• Time-weighted average (standardized AUC) percent change from baseline in biomarkers of bone formation levels in serum over time [Time Frame: Baseline to week 76]</td>
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<td>• Concentration of total activin A in serum over time [Time Frame: Baseline to week 70]</td>
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<td>• PK profile of REGN2477, assessed as concentrations of REGN2477 in serum over time [Time Frame: Baseline to week 76]</td>
</tr>
<tr>
<td></td>
<td>• Immunogenicity of REGN2477 [Time Frame: Baseline to week 76]</td>
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As determined by the incidence, tolerability, and clinical impact of treatment-emergent ADA to REGN2477 over time.
Things to Consider....

- **What is required for study participation and how often?**
  - For example: CT scans, PET scans, X-rays, blood draws, questionnaires, daily entries...
  - How frequently do I need to do these evaluations?
  - What kind of daily activities do I need to record?
  - Where do I need to go to participate in the study?

- **Will study evaluations be shared with me and/or my personal physician?**
  - May have to do same study for routine care

- **How is the drug (or placebo) administered and how frequently?**
  - Intravenous, injection, oral
  - Daily, multiple times per day, weekly injection

- **Other medications**
  - Requirement to stop other medications
  - Medications that are not allowed
Things to Consider....

- **What are the risks associated with participation?**
  - Risks should be clearly addressed in the Informed Consent
    - Ask about safety data or anything that seems unusual in the monitoring or consent

- **Duration of study**
  - Am I planning major life changes that will affect my ability to participate?

- **Who covers the costs of the studies?**
  - Study sponsor, personal insurance, combination?
  - If severe AE happens?

- **Who covers my expenses?**
  - Parking, lunch
  - Study participation often requires missing work - can participation occur after work hours?

- **Specimen Retention**

- **Privacy and Confidentiality**
Specimen Retention or Submission to Centralized Repository

What happens to my tissue, blood or DNA specimen?

• How long is the sponsor required to keep specimens?
• Does the sponsor also keep the specimen for further research?
• Are specimens submitted to a central repository?
  ○ Can be a condition for study funding with rare diseases
• Is there the ability to “opt out” of specimen retention
Privacy and Confidentiality

- **All study staff are obligated to keep personal information private**
  - Study data is kept in secure, locked locations and is password protected
  - Always a potential loss of privacy

- **Medical charts are thoroughly reviewed to determine eligibility**

- **Study participants are anonymized with an ID number**
  - Study participants are referred to by ID number
  - Data transmitted to sponsor is coded with study ID number

- **Sponsor personnel review original medical records and study evaluations for accuracy**

- **Publications are generally about groups and maintain confidentiality**
  - Individuals may be able to be identified in small studies
Responsibilities

- Commitment to the trial
- Do not share studies information including study number
- Always be truthful
- Follow study requirements as stated in the protocol
  - i.e. no retrospective diary entries
- Report all concurrent medications and adverse reactions
Adverse Events (AEs)

Adverse Events are side effects that occur during a clinical trial and may or may NOT be related to treatment

- AEs may be coincidental or directly related to treatment
  - Headaches, dry mouth, dizziness, fainting, seizures

- AEs are classified as Mild / Severe, Related / Unrelated to treatment

- All AEs are recorded, **SEVERE** AEs are reported to the institutional IRB and FDA for safety monitoring

  - Severe AEs may result in discontinuation of the treatment and/or clinical trial
  - The collection of AEs from all participants forms the treatment warnings
  - Study participants must keep a diary of potential AEs and report to the study coordinator
Acknowledgments

- Cindy Morgan, MS, LCGC
Questions???