Protocol #: 19-1362
Project Title: Safety and efficacy of tofacitinib for immune skin conditions in Down syndrome
Principal Investigator: Joaquin Espinosa, PhD
co-PIs: Emily Gurnee, MD; Angela Rachubinski, PhD

Document: Informed Consent Form (ICF)
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You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

If you are making a decision for someone else
Some people in this study may have a medical condition or a disability that does not allow them to make important decisions for themselves. If you have been asked to decide for someone else whether they should be in this study, please read this consent form carefully.

In this form, we use the words "you" and "your." If you are reading this form and deciding for someone else, the words "you" and "your" refer to that person, not to you.

Why is this study being done?
This study plans to learn more about the role of inflammation and the immune system in Down syndrome. This study will also test whether a specific drug, called Tofacitinib, can help treat immune skin conditions in people with Down syndrome. Tofacitinib is a member of a class of drugs, called JAK inhibitors, that modulate the immune system and are being studied for their ability to treat a wide variety of immune conditions. Tofacitinib is FDA-approved for psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis, but not for the immune skin conditions being studied in this clinical trial. As such, the use of Tofacitinib in this study is considered investigational.

You are being asked to be in this research study because you are an individual with Down syndrome who also has an immune skin condition.

Other people in this study
Up to 100 other people with Down syndrome will participate in the study locally.

What happens if I join this study?
If you join the study, you will be asked to complete a series of eight study visits over the course of approximately 4-5 months, including today's visit. Study visits will vary in length from 60 minutes to approximately 4 hours, and a clinical coordinator will work with you to schedule these visits at the appropriate times and explain which procedures will occur at each visit. A study partner must be present with you at all study visits, and we may talk to your study partner about your health and participation in the study.

Today, which is Visit 1, you will be screened for eligibility to participate in the study. This screening involves:

- Physical exam and collection of vital signs by a doctor or nurse

- Skin assessment and diagnosis by a dermatologist
- Mouth swab collection
- Chest x-ray
- Electrocardiogram
- Tuberculosis test
- Pregnancy test (for females)
- A blood draw to assess the following: cytogenetic diagnosis of trisomy 21 (if needed), complete blood counts, standard blood chemistry panels, screening for viral infections, including HIV and hepatitis, and to perform the research described above.
- A hearing test may be performed today or at a follow-up visit

After today's visit, a clinical coordinator will contact you within approximately three weeks to tell you if you are officially eligible to participate in the study. The study doctors may request additional tests or assessments to make sure you are eligible for this study. If you are eligible, and choose to participate, the clinical coordinator will schedule all your study visits and will send you a survey with questions about your demographics and health history to complete before your next visit, Visit 2.

During this time, we will also review your medical records. If you are seen regularly in the University of Colorado Hospital system, we will have access to your electronic medical records. If you see a doctor outside of the University of Colorado Hospital system, we will ask you to complete a Medical Records Request Form, which we will send to your doctor. The health information from your medical records and the survey that you fill out will be entered into a secure database.

Beginning with Visit 2, and each time you return for a study visit, you will undergo a physical exam, collection of vital signs, and a blood draw in order to monitor your overall health throughout the study. Additional activities will take place at various points throughout the study, as detailed in Figure 1 on Page 3. Specifically, at Visit 2, 3, 5, 7, and 8, additional vials of blood will be drawn, and a mouth swab will be collected for the research described above.

At Visit 2, 5, and 7, a dermatologist will again assess your skin condition(s) for research purposes. You will be asked to allow us to take a non-invasive skin tape sample at these visits. Photos of your skin might be taken at any visit to document skin changes, and may be used when we talk about this study to other scientists and to the public. These photos will be deidentified so that your face or identifying marks cannot be seen.

At Visit 2 and 7, you will be asked to complete a series of tasks and questions to tell about how you think and your quality of life. These sessions will be videotaped so the researchers can make sure that we are administering the tests correctly.

At Visit 7, you will have a final hearing test.

The study doctor may recommend additional or more frequent safety screening depending on your situation.

Beginning with Visit 2, we will provide you with a study medication, that you must take twice-per-day, morning and evening, in order to remain in the study. The medication will be the investigational drug, Tofacitinib.

Some participants might not respond to Tofacitinib within the 16-week timeframe. The study doctor may allow the participant to remain in the trial for an additional 24 weeks. You can choose not to continue in the longer trial. You may also receive Tofacitinib from your regular doctor during this time and remain in the study for extra monitoring only. These participants will have additional study visits (at 28-weeks and 40-weeks) for safety monitoring and for research, including an audiogram, and will complete a final round of tasks and questions to tell about how you think and your quality of life.

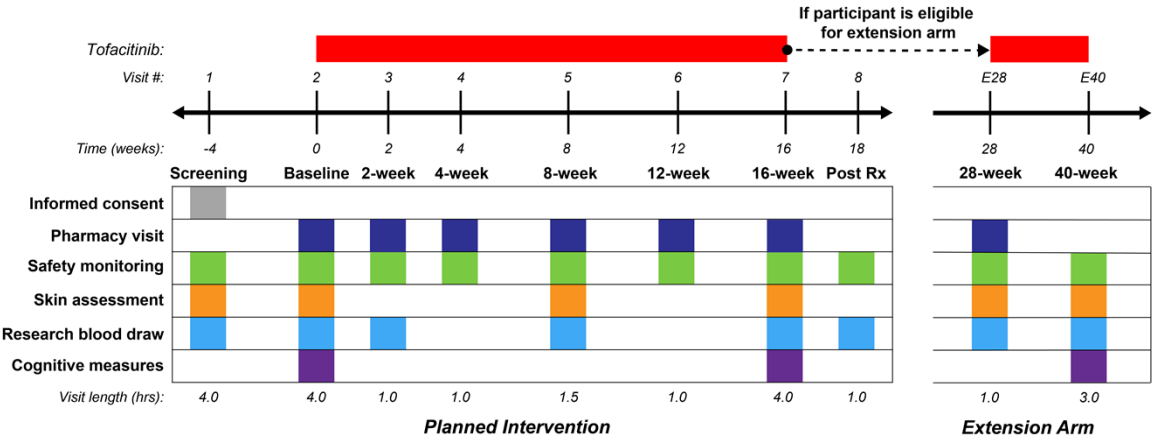

Figure 1 - Schedule of study visits and activities that will take place in this study

It may be more convenient for you to have some laboratory tests drawn nearer to your home. The study team may arrange for a qualified phlebotomist to visit your home, or for you to go to an alternate facility for a blood draw at their discretion. You may be asked to pay for these visits, and the study will re-imburse you when receipts are received. This is not an option for all visits. If you prefer, you can always choose to have your appointments at your regular study site.

No standard medical care will be provided by this study. Only the study drug, Tofacitinib, will be provided. You should continue to see your primary care and other physicians for routine medical care throughout the course of this study, unless directed otherwise. Routine laboratory tests will be incorporated into your University of Colorado Hospital medical record, and we can share some routine laboratory test results with your primary care doctor or other physician if needed for your clinical care with your permission.

The study will keep a linker of your study ID and personal information, but this linker will not be available to other researchers. Your de-identified (no study ID included) or coded information (study ID included, but no personal information) may be shared with other researchers or put into a national database for unrestricted use. Please see page 7 of this consent for additional information. As we are unable to anticipate all new technologies or research questions that may arise during the course of this study, leftover blood samples and data may be used for future, unspecified research related to the stated goals of this study.

You will be given the option to also enroll in the Human Trisome Project Biobank at the Linda Crnic Institute for Down Syndrome (COMIRB 15-2170, PI Joaquin Espinosa). If you choose to enroll, your identified clinical information collected through this study, and any samples leftover at

the conclusion of this study, will be securely transferred to the Human Trisome Project Biobank for use in future research. Participation in the Human Trisome Project Biobank is not required in order to participate in this study.

Even if you choose not to join the Human Trisome Project, you may allow for your leftover samples and de-identified information to be used for future, unspecified research unrelated to this study (see optional procedures).

Optional additional research participation

_____ **Yes,** I give my permission to be contacted in the future to ask me if I would like to take part in more research.

_____ **No,** I do not give my permission to be contacted in the future to ask me if I would like to take part in more research. Please destroy my contact information when no longer needed for this study.

Optional additional consent for future unspecified research

_____ **Yes,** I give my permission for researchers to keep my leftover samples for use in future unspecified research.

_____ **No,** I do not give my permission for researchers to keep my leftover samples for use in future, unspecified research.

Optional additional consent for incidental findings

This study is not designed to give individual results back to the participant. In very rare instances, we may find results about your health that we feel are important for you and your doctor to know. We may require that these results are returned to you through a medical doctor or genetic counselor whom you choose. This requires us to break the study ID linker that protects your privacy.

_____ **Yes,** I give my permission to be contacted with results which the study doctor feels is important for me to know.

_____ **No,** I do not give my permission to be contacted with results which the study doctor feels are important for me to know.

What are the possible discomforts or risks?

Discomforts you may experience while in this study include minor pain during blood draws when the needle goes into your skin, and the possible development of a small bruise at the needle site. You may also experience minor anxiety, fatigue, boredom, or frustration during the completion of the tasks and questions for measuring cognition and quality of life. Some of the questions may be uncomfortable to answer.

This study requires visits to Denver, CO which is at a higher altitude than some out-of-state participants are used to. You should consult your regular care provider if you have any questions about your risks of traveling to a higher altitude and drink plenty of water during your visit.

Other possible risks of participating in this study are associated with the study drug, Tofacitinib. The possible risks and side effects associated with taking Tofacitinib are listed below.

Less common, moderate side effects may include:

- Infections, such as upper respiratory tract infections, nasopharyngitis, and urinary tract infections
- Diarrhea
- Headache
- Hypertension

Rare, mild side effects may include:
- Abnormal blood chemistry or cell counts
- Rash
- Nausea

Rare, but severe side effects may include:
- Serious infections, such as pneumonia, cellulitis, and herpes zoster
- Development of a tear in your stomach or intestines
- Development of blood clots in your legs or lungs
- Development of cancer

In 2021, the Food and Drug Administration (FDA) issued a warning about the safety of Tofacitinib. The warning was in response to a study comparing Tofacitinib to a related drug, called Humira. The study was performed in typical individuals ages 50 years and older with rheumatoid arthritis (RA) who were also taking methotrexate and who had risk factors for cardiovascular disease. The study found an increased risk of serious heart events, cancer, blood clots, and death in people taking Tofacitinib versus Humira over approximately four years. More specifically, the Tofacitinib group had higher rates of cardiovascular events (3.4% vs. 2.5%) and cancer (4.2% vs. 2.9%). Because of these findings, this study excludes participants who are over 50 years old, who are taking methotrexate, or who have recent history of blood clot disorders or cancer. In addition, the study team will also monitor your heart function.

If you become pregnant, Tofacitinib may involve risks to the embryo or fetus which are currently unclear. Therefore, we would ask you to immediately stop taking your study medication and you would be removed from the study.

Finally, there is a risk that people outside of the study team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

What are the possible benefits of the study?
This study is designed for researchers to learn more about inflammation and the immune system in people with Down syndrome. You may experience improvement in your immune skin condition and other autoimmune conditions. However, there is no guarantee that your health will improve if you join this study. Also, there could be risks to being in this study. If there are risks, these are described in the section describing the discomforts or risks, as described above.

Risks and benefits considering COVID-19
This study drug (Tofacitinib) belongs to a group of immunosuppressive drugs called JAK inhibitors.
- In a large study of immunosuppressive drugs and COVID-19 in the general population, the long-term use of JAK inhibitors was linked to a lower risk of death in patients hospitalized with COVID-19.
- Several JAK inhibitors, including Tofacitinib, have been tested for the treatment of COVID-19 in the general population, with positive results.

- The JAK inhibitor Baricitinib is approved by the Food and Drug Administration for the treatment of severe COVID-19 in hospitalized adults requiring supplemental oxygen or ventilation.
- When Baricitinib is not available to treat COVID-19, the National Institutes of Health recommend the use of Tofacitinib instead.
- We will inform you of any new findings that might alter your risk while taking the study drug.

Are there alternative treatments?
There are alternative treatments to your skin condition(s), which you should discuss with your doctor before enrolling in this study, if you have not already done so. For many people, JAK inhibitors, like the one used in this study, are a second line of treatment, if the most commonly accepted treatments do not work. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have other treatment choices available to you.

Who is paying for this study?
This research is being funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) at the National Institutes of Health (NIH).

Will I be paid for being in the study?
You will be paid $25 for each visit in this study. This will add up to a total of $200 if you complete all eight of the standard visits. If you are asked to participant in the Extension Arm of the trial, you will be compensated $25 visit. If you leave the study early, or if we have to take you out of the study, you will be paid only for the visits you have completed. It is important to know that payment for participation in a study is taxable income. You may also be reimbursed for travel expenses.

Will I have to pay for anything?
It will not cost you anything to be in the study, but you may incur travel costs above the reimbursable amount. You may have to pay for additional doctor visits to determine eligibility if the study doctors need more information based on your screening visit results.

Is my participation voluntary?
Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled. If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be removed from this study?
The study doctor may decide to stop your participation without your permission if they think that being in the study may cause you harm, or for any other reason. Also, the sponsor may stop the study at any time.

What happens if I am injured or hurt during the study?
If you have an injury while you are in this study, you should call Dr. David Norris at the UCHealth Dermatology Clinic immediately. The clinic number is 720-848-0500.

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?
The researcher carrying out this study is Dr. Joaquin Espinosa. You may ask any questions you

have now. If you have questions, concerns, or complaints later, you may call Dr. Espinosa at 303-724-7389. You will be given a copy of this form to keep.

You may have questions about your rights as a participant in this study. You can call Dr. Espinosa with questions. You can also call the responsible Institutional Review Board (COMIRB) at 303-724-1055.

A description of this clinical trial is available on http://www.ClinicalTrials.gov, as required by U.S. Law: https://clinicaltrials.gov/ct2/show/NCT04246372. This website does not include information that can identify you. Eventually, the website will include a summary of the results. You can search this website at any time.

This study has been issued a Certificate of Confidentiality from the federal government to help protect your privacy. The Certificate prohibits the researchers from disclosing your name, or any identifiable information, document or biospecimen from the research, with the exceptions listed below. A certificate provides protections against disclosing research information in federal, state, or local civil, criminal, administrative, legislative or other proceedings.

These protections apply only to your research records. The protections do not apply to your medical records.

The researchers may disclose your name or identifiable information, document or biospecimen, under the following circumstances:

- To those connected with the research,
- If required by Federal, State or local laws,
- If necessary for your medical treatment, with your consent,
- For other scientific research conducted in compliance with Federal regulations,
- To comply with mandated reporting, such as a possible threat to harm yourself or others, reports of child abuse, and required communicable disease reporting, or
- Under other circumstances with your consent.

A Certificate of Confidentiality does not protect information you or a member of your family voluntarily release.

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Anschutz
- University of Colorado Hospital
- Children's Hospital Colorado (Children's Colorado)

Children's Colorado shares a medical record system with the Barbara Davis Center and PedsConnect; therefore, it is also possible that other healthcare professionals could view your information.

We cannot do this study without your permission to see, use, and give out your information. You

do not have to give us this permission. If you do not, then you may not join this study.

We will see, use, and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information, but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Dr. Joaquin Espinosa
12700 East 19th Avenue, MS8608
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research.

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator. To ensure proper evaluation of test results, your access to these study results may not be allowed until after the study is completed.

The investigator (or staff acting on behalf of the investigator) will use your information for the research outlined in this consent form. They may also make *all or some* of the following health information about you collected in this study available to: Colorado State University (CSU).

We may share data from our research with other researchers or data banks. One such data bank is called dbGaP, which collects genetic and other data and is sponsored by the National Institutes of Health (NIH). By broadly sharing data in data banks like these, we can make our discoveries more accessible to other researchers, and such samples may be used for any research use. This type of data sharing is required by NIH-funded studies, such as this one. Information which directly identifies you will not be sent to these data banks.

Because your genetic information is unique to you, there is a small risk that someone could connect the information back to you. Also, genetic research and broadly sharing data may involve risks to you or people like yourself that are unknown at this time.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and demographic information (age, sex, ethnicity, address, phone number, etc.)
- Portions of your previous and current medical records that are relevant to this study, including but not limited to diagnosis(es), history and/or physical, laboratory or tissue studies, radiology studies, procedure results.
- Research visit and research test records
- Psychological tests, including cognition assessments and quality of life surveys
- Testing for or infection with diseases reportable to the Public Health department, including but not limited to: Human Immunodeficiency Virus (HIV), hepatitis (all forms), and tuberculosis.
- Tissue samples and the data with the samples.

If you test positive for HIV (Human Immunodeficiency Virus) and/or Hepatitis in this study, we must report your name to the Colorado Department of Public Health and Environment. Finding out that you have HIV or Hepatitis may make it hard for you to get insurance.

What will happen to my recorded information?
In this study we will be recording cognitive assessments and photographs of your skin. We will use digital video recordings on a computer and digital photographs. We will keep this information secure and private. We will store it for up to 50 years. At the end of that time, we will destroy it.

What happens to data, tissue, blood and specimens that are collected in this study?
Scientists at the University of Colorado Anschutz and the hospitals involved in this study work to find the causes and cures of disease. The data, tissue, blood and specimens collected from you during this study are important to this study and to future research. If you join this study:

- The data, tissue, blood, or other specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data, tissue, blood, or other specimens collected from you.
- If data, tissue, blood, or other specimens are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

HIPAA Authorization for optional additional study procedures
In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study.

Please initial next to your choice:

_____ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____ I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

Agreement to be in this study and use my data
I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature:_____ Date: _____

Print Name:_____

If required, Legally Authorized Representative/Medical Durable Power of Attorney for Health Care Holder:

Signature:_____ Date: _____

Print Name:_____

For non-reading subjects or those consented using the Short Form:

Signature:_____ Date: _____

Print Name:_____

Witness of signature □

Witness of consent process □

For study staff use only:

Consent form explained by: _____ Date: _____

Printed name: _____