Dupilumab for the Treatment of Moderate-to-severe, Chronic Hepatic Pruritus: An Open-label, Single-arm, Exploratory Study

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DUPILUMAB FOR THE TREATMENT OF MODERATE TO SEVERE CHRONIC HEPATIC PRURITUS: AN OPEN-LABEL, SINGLE-ARM, EXPLORATORY STUDY

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Product:	Dupilumab (Dupixent)
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List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CLDQ	Chronic Liver Disease Questionnaire
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IL-4	Interleukin-4
IL-13	Interleukin-13
IND	Investigational New Drug Application
INR	International Normalized Ratio
IRB	Institutional Review Board
ISR	Injection Site Reaction
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SC	Subcutaneous
SOP	Standard Operating Procedure
VAS	Visual Analogue Scale
VRS	Visual Rating Scale
PNRS	Pruritus Numerical Rating Score

Study Summary

Title	Dupilumab for the treatment of moderate to severe chronic hepatic pruritus: An open-label, single-arm, exploratory study
Running Title	Dupilumab for chronic hepatic pruritus
Protocol Number	*19-002757*
Phase	Phase II
Methodology	Open-label, single-arm, exploratory study
Overall Study Duration	18 months
Subject Participation Duration	22 weeks
Single or Multi-Site	Single-Mayo Clinic Florida
Objectives	To investigate the potential efficacy of dupilumab in the treatment of moderate to severe chronic hepatic pruritus.
Number of Subjects	12
Diagnosis and Main Inclusion Criteria	Male and/or female subjects 18 years or older with chronic pruritus of moderate to severe severity in the setting of intrahepatic or extrahepatic cholestatic liver disease. Chronic is defined as greater than 6 weeks of symptom duration. Pruritus severity is based on the peak pruritus numerical rating score (PNRS) of 4 (moderate severity).
Study Product, Dose, Route, Regimen	Dupilumab 600 mg SC week 0; then every 2 weeks x 18 weeks
Duration of Administration	18 weeks
Reference therapy	None-open label use of study drug
Statistical Methodology	A paired t-test will be used to evaluate mean differences before and after treatment at a p=0.05 significance level. The primary endpoint of the study is the mean percent change from baseline peak pruritus numerical rating score (PNRS) after 18 weeks. Correlations between the percent mean changes in the PNRS and quality of life outcome measures will also be analyzed.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Chronic pruritus secondary to liver disease can negatively impact quality of life. These patients characteristically lack any skin inflammation, but are often severely symptomatic with chronic generalized involvement leading to significant quality life impairments in sleep, daily activities, and personal relationships. To date, no clear pathophysiologic mechanism has been elucidated in chronic hepatic pruritus. No correlation has been found between plasma bile salt levels and endogenous opioid levels; while serum autotaxin levels are elevated in cholestatic liver disease, they are also increased in other pathological conditions which are not associated with pruritus. Standard therapy with bile salt binders, rifampin, sedating anti-histamines, partial opioid antagonists, selective serotonin reuptake inhibitors, narrowband UVB phototherapy, and serum plasma exchange is frequently ineffective and associated with dose limiting side effects. There exists a significant unmet clinical need for new therapies in the management of chronic hepatic pruritus.

1.2 Investigational Agent

Dupilumab, a licensed, FDA approved treatment for Atopic Dermatitis, is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Ra subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab is a clear to slightly opalescent, colorless to pale yellow solution available as an injection of 300 mg/2 mL in a single-dose pre-filled syringe with needle shield for subcutaneous administration. Published results consistently showed that, compared with placebo, subcutaneous dupilumab 300 mg once weekly (qw) or every 2 weeks (q2w) significantly improved objective signs and symptoms of AD including pruritus, symptoms of anxiety and depression, and quality of life using dermatology-specific measures.

1.3 Preclinical Data

Recently, it has been established that IL-4 and IL-13 may directly activate sensory neurons in both mouse and human experimental models. Additionally, small diameter neurons mediating pruritus have been found to be enriched with IL-4 receptors and IL-13 receptors compared to other families of nociceptive and mechanoreceptive neurons. IL-4 has also been established to sensitize neurons to respond to previously subthreshold levels of histamine as well as other endogenous pruritogens. Therefore, inhibition of IL-4/IL-13 cytokine signaling on sensory neurons represents a potential therapeutic target in other conditions with chronic pruritus without overt skin inflammation.

1.4 Clinical Data to Date

Dupilumab, a fully human monoclonal antibody that blocks interleukin-4 and interleukin-13, has shown efficacy in the treatment of pruritus associated with moderate to severe atopic dermatitis. Notably, improvement of pruritus usually precedes clinically significant skin clearance suggesting other mechanisms beyond direct anti-inflammatory effects are of importance. Therefore we propose that dupilumab may have drug anti-pruritic effects independent of inflammatory effects.

1.5 Dose Rationale

The dose regimen of subcutaneous (SC) dupilumab selected for this study is 300 mg every 2 weeks for 18 weeks. All patients will get an initial loading dose of 600 mg (given as two 300 mg injections) at week 0. The administration of the loading dose of dupilumab will allow systemic concentrations to reach steady-state faster and reduce the time to onset of clinical effect. The dose of dupilumab for this study was based on the efficacy and safety results from multiple clinical trials that have led to the FDA approval of dupilumab at an initial dose of 600 mg then 300 mg every 2 weeks, for 18 weeks, for the treatment of atopic dermatitis.

1.6 Risks and Benefits

The postulated benefits of dupilumab include sustained immunomodulatory effects resulting in improvement of chronic hepatic pruritus. Mechanistically, as a biologic class medication, dupilumab has no hepatic metabolism; and since FDA approval for atopic dermatitis and asthma, no incidents of hepatic impairment have been reported

The following risks of dupilumab therefore felt to be low and manageable with the study protocol and do not outweigh the aforementioned benefits:

<u>Hypersensitivity Reactions</u>
Hypersensitivity reactions, including generalized urticaria and serum sickness or serum sickness-like reactions were reported in less than 1% of subjects who received dupilumab in clinical trials. This risk is idiosyncratic and will be minimized by administrating dupilumab in a supervised medical setting for the first treatment dose.

<u>Conjunctivitis and Keratitis</u>
Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received dupilumab. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis recovered or were recovering during the treatment period. Among asthma subjects the frequency of conjunctivitis was similar between dupilumab and placebo. Therefore, the development of keratitis appears related to the pathophysiologic state of AD and may not be entirely a direct drug effect. Keratitis was reported in <1% of the dupilumab group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52 week dupilumab + topical corticosteroids (TCS) atopic

dermatitis trial, keratitis was reported in 4% of the dupilumab + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with keratitis recovered or were recovering during the treatment period. Among asthma subjects the frequency of keratitis was similar between dupilumab and placebo. Subjects will be advised to report new onset or worsening eye symptoms and will be appropriately assessed and treated.

Eosinophilic Conditions
Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with dupilumab in adult patients who participated in the asthma development program. A causal association between dupilumab and these conditions has not been established.

Reduction of Corticosteroid Dosage
Reductions in corticosteroid dose, if appropriate, will be gradual and performed under the direct supervision of a physician.

Parasitic (Helminth) Infections
Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if dupilumab will influence the immune response against helminth infections. This risk will be minimized by excluding enrollment of study participants with known tapeworm or roundworm infections.

2 Study Objectives

Primary Objective: To investigate the potential efficacy of dupilumab in the treatment of adults with moderate to severe chronic hepatic pruritus.

3 Study Design

3.1 General Description

This is a 22-week (2 week screening, 18-week treatment period followed by a 2 week follow-up), phase II, open label, exploratory study to investigate the potential efficacy of FDA approved dupilumab in the treatment of adults with moderate to severe chronic hepatic pruritus. Subjects will be screened at outpatient clinic visit appointments and interested qualified subjects will be consented and offered participation in this trial. Once consent has been obtained, baseline values will be established and subjects will begin treatment and follow-up for the next 20 weeks. A final visit will be needed for evaluation and questionnaire completion.

3.2 Number of Subjects

A target of 12 subjects will be enrolled.

3.3 Duration of Participation

Each subject's participation in the study will be up to 22 weeks including the screening period.

3.4 Primary Study Endpoints

The primary endpoint of the study will be the mean percent change in the Peak Pruritus Numerical Rating Score (PNRS) before and after 20 weeks of treatment with dupilumab. Pruritus severity is measured using the peak NRS assessed as a single, self-completed item that assesses the intensity of peak (worst) pruritus during the past 24 hours using the query: "On a scale of 0 to 10, with 0 being 'no itch 'and 10 being 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?". The baseline and treatment mean peak PNRS will be the average of the daily score for 7 days before treatment and then after the first treatment dose self-assessed by patients daily and then averaged for 7 days.

3.5 Secondary Study Endpoints

The other secondary endpoints regarding pruritus will be assessed at baseline and as follows:

1. Percentage of patients with an improvement in weekly average PNRS 3 from baseline. This will be assessed at week 6,12,18
2. Percentage of patients with an improvement in weekly average PNRS 4 from baseline. This will be assessed at week 6,12,18
3. Mean change in the verbal rating scale (VRS) of pruritus as measured 0=none; 1= mild; 2=moderate; and 3=severe/intense. This will be assessed at week 6,12,18
4. Mean change of 5D pruritus score. This is a multidimensional questionnaire designed to assess the degree, duration, direction, disability and distribution of pruritus longitudinally with scoring ranging from 5=no pruritus/well-controlled to 25=severe pruritus/poorly controlled. This will be assessed at baseline and at week 18.
5. Chronic Liver Disease Questionnaire (CLDQ). This is a validated quality life instrument for patients with chronic liver disease evaluating systemic symptoms, fatigue, physical activity, emotional function, and worry using a 7 point scale with 1=all of the time; 2=most of the time; 3=a good bit of the time; 4=some of the time; 5=a little of the time; 6=hardly any of the time; and 7=none of the time. This will be assessed at baseline and week 18.

3.6 Primary Safety Endpoints

This is an exploratory efficacy study with no specific primary safety endpoint. Adverse events will be tracked and reported using Good Clinical Practice standards and as described in Section 8 of this protocol.

The safety of dupilumab in this population will be assessed by evaluating the detailed medical history through physical examination, vital signs, and clinical laboratory testing. Concomitant medications and procedures will be collected from time of informed consent to the end of the study.

3.7 Identification of Source Data

The following source data will be directly recorded on the Case Report Form (CRF):

- Screening and documentation of adverse events
- Confirmation of patient counseling and education
- PNRS score
- VRS score
- 5D Pruritus Score
- CLDQ questionnaire

The following source data will not be directly recorded in the CRF, but will be captured in supportive documentation to include study source documents and the EMR:

- Laboratory results and clinical interpretation of the values

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

Subjects who meet the following criteria will be considered eligible to participate in the clinical study:

1. Male and/or female subjects 18 years or older with chronic pruritus of moderate to severe severity in the setting of intrahepatic or extrahepatic cholestatic liver disease. Chronic is defined as greater than 6 weeks of symptom duration. Pruritus severity is based on the peak pruritus numerical rating score of 4 (moderate severity).
2. Documentation of a personally signed and dated informed consent indicating that the subject or their legally acceptable representative has been informed of all pertinent aspects of the trial.
3. Willingness and ability to comply with scheduled clinic visits, physical exams, laboratory tests, questionnaires, effective contraception use, and other trial procedures.

4.2 Exclusion Criteria

Subjects who meet one or more of the following criteria will not be considered eligible to participate in the clinical study:

1. Male and/or female subjects under 18 years of age.
2. Pruritus due to a primary inflammatory skin dermatosis or other forms of psychogenic pruritus utilizing skin biopsies as needed.
3. Pregnant females

4. History of intrahepatic cholestasis of pregnancy
5. Any form of chronic hepatic pruritus associated with underlying malignancy
6. Liver transplant recipients
7. Allergy to dupilumab or its ingredients
8. Inability to provide informed consent
9. Concomitant use of selective opioid antagonists
10. Subjects with severe asthma (requiring high-dose inhaled or systemic corticosteroids) will be excluded from the study.
11. Patients with known helminth infections

4.3 Subject Recruitment, Enrollment and Screening

Subjects will be recruited from a single, tertiary-care facility from the principal investigator and/or co-investigator clinical practices located in the departments of dermatology, gastroenterology and hepatology, and transplantation at Mayo Clinic in Florida. Potential subjects will be screened to confirm a diagnosis of chronic hepatic pruritus based on clinical evaluation and documentation of inclusion/exclusion criteria. Patients will be provided with a Research Participant Consent and Privacy Authorization Form describing the study drug, protocol, inclusion and exclusion criteria, as well as risks and benefits of participation.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Patients are free to withdraw at any time and for whatever reason. No data will be collected for withdrawn subjects. Withdrawn subjects may be replaced within the accrual period. There will be no follow-up for withdrawn subjects. Pre-specified reasons for discontinuing include, but are not limited to, the following:

- Patient Request: Patient decided that he/she did not want to continue (for any reason)
- Sponsor/Principal Investigator Request: Patients may be withdrawn from the study for any reason, at the discretion of the Sponsor/PI.
- Adverse Event: Patient experienced a related or unrelated event that would interfere with the study objectives/evaluation
- Lost to Follow-up: Patient did not come in for a visit and could not be reached by phone
- Treatment Failure: If in the Principal Investigator and/or Investigators' judgment, the patient's condition required another form of treatment
- Inclusion/Exclusion Discrepancy/Violation: Patient should not have been enrolled
- Noncompliance: Patient is not complying with the protocol requirements (i.e. visit schedule, dosing, regimen, etc.); a patient is to be withdrawn if he/she misses two consecutive visits
- Other: Any other reason

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a participant withdraws from the study, no additional attempts will be made to contact the participant.

5 Study Drug

Dupilumab is FDA approved to treat adults with moderate-to-severe atopic dermatitis (eczema) that is not well controlled with prescription therapies used on the skin (topical), or who cannot use topical therapies. Dupilumab can be used with or without topical corticosteroids. It is not known if Dupilumab is safe and effective in children with atopic dermatitis under 18 years of age.

Dupilumab is FDA approved to treat adults with other asthma medicines for the maintenance and treatment of moderate-to-severe asthma in people aged 12 years and older whose asthma is not controlled with their current asthma medicines. Dupilumab helps prevent severe asthma attacks and may also help reduce the amount of oral corticosteroids need while preventing severe asthma attacks. Dupilumab is not used to treat sudden breathing problems. It is not known if Dupilumab is safe and effective in children with asthma under 12 years of age.

5.1.1 Mechanism of Action

Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Ra subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor. Blocking IL-4Ra with dupilumab inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, including the release of pro-inflammatory cytokines, chemokines, nitric oxide, and IgE.

5.1.2 Pharmacodynamics

Consistent with receptor blockade, serum levels of IL-4 and IL-13 were increased following dupilumab treatment. The relationship between the pharmacodynamic activity and the mechanism(s) by which dupilumab exerts its clinical effects is unknown.

5.1.3 Pharmacokinetics

Absorption: Following an initial subcutaneous (SC) dose of 600 mg, dupilumab reached peak mean ±SD concentrations (Cmax) of 70.1±24.1 mcg/mL by approximately 1 week post dose.
Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose either weekly (twice the recommended dosing frequency) or every other week. Across clinical trials, the mean ±SD steady-state trough concentrations ranged from 73.3±40.0 mcg/mL to 79.9±41.4 mcg/mL for 300 mg administered every 2 weeks and from 173±75.9 mcg/mL to 193±77.0 mcg/mL for 300 mg administered weekly. The bioavailability of dupilumab following a SC dose is estimated to be 64%.

Distribution: The estimated total volume of distribution was approximately 4.8±1.3 L.

Elimination: The metabolic pathway of dupilumab has not been characterized. As a human monoclonal IgG4 antibody, dupilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. After the last steady-state dose of 300 mg Q2W or 300 mg QW dupilumab, the median times to non-detectable concentration (<78 ng/mL) are 10 and 13 weeks, respectively.

Dose Linearity: Dupilumab exhibited nonlinear target-mediated pharmacokinetics with exposures increasing in a greater than dose-proportional manner. The systemic exposure increased by 30-fold when the dose increased 8-fold following a single dose of dupilumab from 75 mg to 600 mg (i.e., 0.25times to 2-times the recommended dose).

Weight: Dupilumab trough concentrations were lower in subjects with higher body weight.

Immunogenicity: Development of antibodies to dupilumab was associated with lower serum dupilumab concentrations. A few subjects who had high antibody titers also had no detectable serum dupilumab concentrations.

Specific Populations:
Geriatric Patients
In subjects who are 65 years and older, the mean ±SD steady-state trough concentrations of dupilumab were 69.4±31.4 mcg/mL and 166±62.3 mcg/mL, respectively, for 300 mg administered every 2 weeks and weekly. No dose adjustment in this population is recommended.

Renal or Hepatic Impairment
No formal trial of the effect of hepatic or renal impairment on the pharmacokinetics of dupilumab was conducted.

Drug Interaction Studies: Drug interaction studies have not been conducted with dupilumab.

5.2 Treatment Regimen

All study participants will receive dupilumab 600 mg SC at week 0; then 300 mg SC every 2 weeks for a total of 18 weeks.

5.3 Method for Assigning Subjects to Treatment Groups

This is an open-label pilot investigation and all study participants are assigned to active treatment. There is no placebo arm in this study.

5.4 Preparation and Administration of Study Drug

The study drug will be stored and dispensed at the first study visit from the Mayo Clinic Research Pharmacy in Jacksonville, FL. Subsequent doses of the study drug will be self-administered by the subject until completion of the study.

For subjects willing and able to self-administer or have a caregiver administer the study drug outside the clinic, the study staff will train the subject/caregiver on preparation and administration of study drug. Subjects who prefer to have clinic staff administer study drug may choose to have injections administered in the clinic.

The procedure for preparing the dupilumab dose for SC injection will be provided in the pharmacy manual. Subcutaneous injection sites should be alternated among the different quadrants of the abdomen, upper tights, and upper arms, so that the same site is not injected for 2 consecutive weeks. To allow for adequate assessment of possible injection site reactions (ISRs), study drug should be administered only into areas of normal-looking skin. Instructions for recording and reporting of ISRs will be provided in the study reference manual.

Detailed instructions for transport, storage, preparation, and administration of study drug will be provided by the site to the patient (or caregiver).

5.5 Subject Compliance Monitoring

All drug accountability records must be kept current. The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication: dispensed to each patient, returned from each patient (if applicable), and disposed of at the site or returned to the sponsor or designee. All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study. All drug compliance records must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors. Patients will complete a dosing diary to document compliance with self-injection of study drug.

Any subject who is significantly non-compliant with the study drug regimen may be withdrawn from the study.

5.6 Prior and Concomitant Therapy

Treatment with live (attenuated) vaccines, investigational drugs (other than dupilumab), or selective opioid antagonists are prohibited for patients actively enrolled onstudy.

Treatment with concomitant medications for chronic hepatic pruritus except for selective opioid antagonists is permitted during the study. This includes basic skin care (cleansing and bathing), emollients, topical anesthetics, and antihistamines for any duration. Medications used to treat chronic disease such as diabetes, hypertension, and asthma are also permitted; if there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the medical monitor.

5.7 Packaging

Dupilumab injection is a clear to slightly opalescent, colorless to pale yellow solution, supplied in single-dose pre-filled syringes with needle shield. Each pre-filled syringe with needle shield is designed to deliver 300 mg of dupilumab in 2 mL solution. Dupilumab is available in cartons containing 2 pre-filled syringes with needle shield.

Pre-filled syringes will be shipped to the Mayo Clinic Research Pharmacy in Florida and then labeled upon receipt with statement "Caution: New Drug Limited by Federal law for investigational use."

5.8 Masking/Blinding of Study

This is an open-label pilot investigation. Masking and blinding procedures are not applicable. Qualitative and quantitative evaluations of response to treatment will be recorded.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

The drug will be shipped by Regeneron Pharmaceuticals to the Mayo Clinic Research Pharmacy in Florida. Upon receipt, an inventory will be performed and a drug receipt log filled out by the person accepting the shipment. Designated study staff will count and verify that the shipment contains all the items noted in the shipping invoice. Any discrepancies, damaged or unusable study drug in a given shipment will be documented in the study files. The sponsor-investigator must be notified immediately of any discrepancies, damaged or unusable products that are received.

5.9.2 Storage

Dupilumab should be stored refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. If necessary, pre-filled syringes may be kept at room temperature up to 77°F (25°C) for a maximum of 14 days. Dupilumab should not be stored above 77°F (25°C). After removal from the refrigerator, dupilumab must be used within 14 days or discarded. The syringe should not be exposed to heat or direct sunlight.

5.9.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on tracked using the Vestigo electronic ledger system. Drug dispensation will occur at the first treatment visit.

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be documented and investigated, prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Visit 1 (Week -2/Screening & Enrollment)

After the subject has provided written informed consent, the following information will be collected:

1. Informed consent
2. Inclusion and exclusion criteria
3. Medical history

The following procedures and assessments will be conducted:

1. PRNS score
2. Laboratory samples including; CBC with differential, AST, ALT, INR
3. Dispense pruritus scoring journal; review instructions

6.2 Visit 2 (Week 0+7 days Baseline)

The following information will be collected:

1. Inventory of existing medications and procedures

The following procedures and assessments will be conducted:

1. Vital signs including; height, weight, body temperature, blood pressure, pulse rate
2. Physical examination

3. Dispense study drug, 12 week supply of dupilumab
4. Instruct subject on self-injection of study drug
5. Observe subject injection technique
6. Review pruritus daily scoring journal; review instructions
7. PRNS score
8. VRS score
9. CLDQ questionnaire

6.3 Visit 3 (Week 6± 5 days)

The following information will be collected:

1. Inventory of existing medications and procedures

2. Adverse events

The following procedures and assessments will be conducted:
1. PNRS score; collect pruritus scoring journal
2. VRS score
3. Vital signs including; height, weight, body temperature, blood pressure, pulse rate
4. Physical examination
5. Laboratory samples including; CBC with differential, AST, ALT, INR
6. Dispense pruritus scoring journal; review instructions

6.4 Visit 4 (Week 12± 5 days)

The following information will be collected:
1. Inventory of existing medications and procedures
2. Adverse events

The following procedures and assessments will be conducted:
1. PNRS score; collect pruritus scoring journal
2. VRS score
3. Vital signs including; height, weight, body temperature, blood pressure, pulse rate
4. Physical examination
5. Laboratory samples including; CBC with differential, AST, ALT, INR
6. Dispense pruritus scoring journal; review instructions
7. Dispense study drug 6 week supply of dupilumab

6.5 Visit 5 (Week 18+2 days)

The following information will be collected:
1. Inventory of existing medications and procedures
2. Adverse events

The following procedures and assessments will be conducted:
1. PNRS score; review pruritus scoring journal
2. VRS score
3. CLDQ questionnaire
4. 5D itch score questionnaire
5. Vital signs including; height, weight, body temperature, blood pressure, pulse rate
6. Physical examination
7. Laboratory samples including; CBC with differential, AST, ALT, INR

6.6 Visit 6-Follow-up (Week 20±5 days)

The following information will be collected:

1. Inventory of existing medications and procedures
2. Adverse events

The following procedures and assessments will be conducted:

1. PNRS post-treatment score; collect pruritus scoring journal

TABLE OF EVENTS SUMMARY						
Week	**Wk -2** Screening Enrollment	**Wk 0** Baseline	**Wk 6 ± 5 days**	**Wk 12 ± 5 days**	**Wk 18 ± 2 days**	**Wk 20 ± 5 days**
Visit	**1**	**2**	**3**	**4**	**5**	**6**
Consent/Enroll	X					
Medical History	X	X	X	X	X	
Dispense Drug		X		X		
Dispense Pruritus Log	X		X	X		
Vital Signs	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X
PNRS	X	X	X	X	X	X
VRS		X		X	X	
5D Pruritus		X			X	
CLDQ		X			X	
CBC with diff	X		X	X	X	
AST/ALT	X		X	X	X	
PT/INR	X		X	X	X	
AE Event Screen		X	X	X	X	X

7 Statistical Plan

7.1 Sample Size Determination

No formal power analysis was performed as this is a pilot study; however, the open-label study design aids in the detection of therapeutic efficacy given the well-established natural history of chronic hepatic pruritus that at baseline has been characterized as persistent, severe, and not association with a natural history of spontaneous improvement.

7.2 Statistical Methods

Descriptive Statistics

Continuous variables will be summarized using the sample mean, median, standard deviation, interquartile range, and range. Categorical variables will be summarized using number and percentage of patients.

Handling of Missing Data

In the event of any unexpected missing data, this will be imputed using the last observation carried forward method.

Multiplicity

Since this is an exploratory pilot study, no adjustment for multiple testing will be undertaken.

Primary Hypothesis: For subjects with chronic hepatic pruritus, treatment with dupilumab will improve the PRNS after 1 weeks of treatment.

As previously described, the PRNS will be assessed on a daily basis for each patient. Separately for the 7 days prior to treatment (i.e. pre-treatment), the first 6 weeks of treatment (i.e. weeks 1 to 6), the second six weeks of treatment (i.e. weeks 7 to 12), the third six weeks of treatment (i.e. weeks 13 to 18), and the final two weeks of treatment (i.e. weeks 19 and 20), the mean of these daily PRNS measures will be calculated for each patient, resulting in a pre-treatment, week 6, week 12, week 18, and week 20 mean PRNS measurement for each patient. We will summarize the percentage change in PRNS values from pre-treatment to week 6, week 12, week 18, and week 20 using the aforementioned descriptive statistics. Additionally, we will estimate the proportion of patients whose mean PRNS value improves by 3 or more point, and by 4 or more points, from pre-treatment to each of the week 6, week 12, week 18, and week 20 time periods. Comparisons of mean PRNS between the pre-treatment time period and each of the week 6, week 12, week 18, and week 20 time periods will be made using a paired Wilcoxon signed rank test.

For secondary endpoints (VRS, 5D pruritus score, and CLDQ), these will be compared between the pre-treatment and follow-up time points using a paired Wilcoxon signed rank test. Although focus will be more on descriptive summaries rather than statistical significance due to the pilot nature of the study, p-values less than 0.05 will be considered as statistically significant.

Interim Analysis

There will not be any interim analysis given the low risk profile of the study formulation and the pilot nature of the study.

7.3 Subject Population(s) for Analysis

Each participant who received the study drug will be included in the primary analysis regardless of study withdrawal for any reason. In the event of any study withdrawals, for any secondary analysis, we will examine the sensitivity of our results to the exclusion of patients who withdrew.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event
An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event
Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity
- birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as the last scheduled visit.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values

Any clinical laboratory abnormality that can reasonably be related to the administration of dupilumab should be documented as an adverse event.

Hospitalization, Prolonged Hospitalization or Surgery

Hospitalization, prolonged hospitalization, or surgery is to be reported as an adverse event if it can reasonably be related to use of dupilumab.

8.2 Recording of Adverse Events

At each contact with the subject, the study team will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results will be recorded in the source document.

All adverse events occurring during the study period will be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The Principal Investigator and/or Investigators will report, as soon as possible, but no later than 5 working days after first learning of the problem/event, to the Mayo Clinic IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo Clinic IRB Policy and Procedures.

Documentation of adverse events will include the following information collected in the adverse event section of the case report form (and entered into the research database):

- Subject's name:
- Medical record number:
- Disease:
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research:
- If the adverse event was expected:
- The severity of the adverse event (defined by a severity scale):
- If any intervention was necessary:
- Resolution (was the incident resolved spontaneously, or after discontinuing treatment):
- Date of Resolution:

The Principal Investigator and/or Investigators will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The Principal Investigator and/or Investigators will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

8.3.2 Sponsor-Investigator reporting: Notifying the FDA

This protocol is not being conducted under an FDA investigational new drug application.

8.4 Unmasking/Unblinding Procedures

This is an open-label pilot investigation. Unmasking and unblinding procedures are not applicable.

8.5 Stopping Rules

This investigation is of low risk to study subjects. Stopping or interruption of the study may be necessary if a significant number of study participants develop unexpected clinical flaring or significant worsening that appears temporally linked with dupilumab administration.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects'

diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

All data requested on the Case Report Form (CRF) will be recorded for each participant. A standardized CRF will be generated by REDCap. All missing data will be explained. If a space on the CRF is left blank because the question was not asked, "N/D" will be recorded. If the item is not applicable to the individual case, "N/A" will be recorded. All entries will be printed legibly in black ink. If any entry error has been made, a single straight line through the incorrect entry will be drawn and the correct data will be written above it. All such changes will be initialed and dated. Errors will not be erased or whited-out. For clarification of illegible or uncertain entries, a clarification will be printed above the item, then initialed and dated. If the reason for the correction is not clear or needs additional explanation, details to justify the correction will be neatly included.

Data Management

Study data will be collected and managed using REDCap electronic data capture tools hosted at the Mayo Clinic. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Data Processing

All study data will be stored and analyzed at Mayo Clinic in Florida using the REDCap electronic data capture tool.

Data Security and Confidentiality

All source documents including clinical findings, observations or other activities will be stored in a REDCap database that will be designed by the Statistician. Access to the REDCap database will be limited to the Principal Investigator, Investigators, and Statistician.

Data Quality Assurance

Once the study is completed the Principal Investigator will randomly select 3 participants and compare the data documented for each on the CRF with what is entered into the REDCap database. If there is any discrepancy, the Principal Investigator and/or Investigators will cross-reference all 12 patients to ensure accuracy.

Data Clarification Process

For any data query the Principal Investigator and Investigators will meet to clarify the data queried and make corrections based on consensus.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for;

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual -"Retention of and Access to Research Data Policy"[redacted]

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent. This study will not include vulnerable study populations.

12 Study Finances

12.1 Funding Source

This investigator initiated study is funded by a research grant from Regeneron Pharmaceuticals to Mayo Clinic.

12.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

No financial conflicts of interested are anticipated or have been identified for this study.

12.3 Subject Stipends or Payments

No payment is given to study participants.

13 Publication Plan

The primary responsibility for publication of the study results is with the Primary Investigator. After the complication of study and prior to publication, the study results will be shared with Regeneron Pharmaceuticals. The study will be registered at ClinicalTrials.gov prior to subject recruitment along with the posting of the results within 12 months of final data collection for the primary outcome measure.

We anticipate the data collected in this study will result in a publishable manuscript and could also support a larger trial if the results are favorable to the proposed hypothesis.

14 References

1. Beck, L. A., et al. (2014). "Dupilumab treatment in adults with moderate-to-severe atopic dermatitis." N Engl J Med 371(2): 130-139.
2. Oetjen, L. K., et al. (2017). "Sensory Neurons Co-opt Classical Immune Signaling Pathways to Mediate Chronic Itch." Cell 171(1): 217-228 e213.
3. Wong, L. S., et al. (2017). "Inflammatory and Noninflammatory Itch: Implications in Pathophysiology-Directed Treatments." Int J Mol Sci 18(7).
4. Ikoma, A., et al. (2003). "Neuronal sensitization for histamine-induced itch in lesional skin of patients with atopic dermatitis." Arch Dermatol 139(11): 1455-1458.
5. Wang, H. and G. Yosipovitch (2010). "New insights into the pathophysiology and treatment of chronic itch in patients with end-stage renal disease, chronic liver disease, and lymphoma." Int J Dermatol 49(1): 1-11.
6. Bhalerao, A. and G. S. Mannu (2015). "Management of pruritus in chronic liver disease." Dermatol Res Pract 2015: 295891.
7. G. Yosipovitch (2017). "Validation of the peak pruritus numerical rating scale: Results from clinical studies of dupilumab in adult patients with moderate-to-severe atopic dermatitis." Journal of the American Academy of Dermatology 76(6): AB278.
8. Kido-Nakahara, M., et al. (2015). "Comparative cut-off value setting of pruritus intensity in visual analogue scale and verbal rating scale." Acta Derm Venereol 95(3): 345-346.
9. Phan, N. Q., et al. (2012). "Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus." Acta Derm Venereol 92(5): 502-507.
10. Elman, S., et al. (2010). "The 5-D itch scale: a new measure of pruritus." Br J Dermatol 162(3): 587-593.
11. Orr, J. G., et al. (2014). "Health related quality of life in people with advanced chronic liver disease." J Hepatol 61(5): 1158-1165.
12. Younossi, Z. M., et al. (1999). "Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease." Gut 45(2): 295-300.

15 Attachments

None