A randomized, double blind placebo-controlled multicenter study of the efficacy and safety of dupilumab in patients with moderate to severe hand eczema refractory to highly potent topical corticosteroids

DUPECZEMAIN

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BIOMEDICAL RESEARCH PROTOCOL

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HISTORY OF REVISIONS TO THE PROTOCOL

VERSION	DATE	REASON FOR THE REVISION
1.1	July 20, 2017	Draft 1 protocol
1.2	December 4, 2017	Draft 2 protocol
1.3	January 4, 2018	Draft 3 protocol
1.4	June 15, 2018	Draft 4 protocol
1.5	July 13, 2018	Draft 5 protocol
1.6	July 20, 2018	Draft 6 protocol submitted to CPP and ANSM
1.7	October 22, 2018	Draft 7 protocol after ANSM question
1.8	November 07, 2018	Version 8 protocol after CPP question
2.0	September 06 2019	Version of 1st substantial modification
2.1	November 18, 2019	Version of 1st substantial modification after CPP and ANSM questions
3.0	June 05, 2020	Version of 2nd (non) substantial modification after Covid crisis
4.0	December 04, 2020	Version of 3th substantial modification
5.0	April 19, 2022	Version of 4th substantial modification
6.0	June 26, 2023	Version of 5th substantial modification

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CONTENTS

List of abbreviations

AD: atopic dermatitis

AE: adverse eventAESI : adverse event of special interest

CRFs: Case report forms

CCTIRS: Consultative Committee on Data Processing in Research in the Area of Health

CHE: chronic hand eczema

CNIL: National Commission for Computing and Civil Liberties

DLQI: Dermatology Life Quality Index

EASI: Eczema Area and Severity Index

EQ-5D-5L: Euroquol-5D questionnaire

FLG: Filaggrin

IGA: Investigator's global assessment

ITT: Intention-To-Treat

LOCF: Last-observation-carry-forward

MedDRA: Medical Dictionary for Regulatory Activities

mTLSS: modified total lesion symptom score

PP: Per-Protocol

PGA: Patient's global assessment

VAS: Visual Analogic Scale

SAE: serious adverse event

SUSAR: Suspected Unexpected Serious Adverse Reaction

WPAI: Work Productivity and Activity Index

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2. SUMMARY OF THE RESEARCH STUDY

SPONSOR	*Toulouse University Hospital*
COORDINATING/PRINCIPAL INVESTIGATOR	*Marie Tauber, MD* *Department of Dermatology Larrey Hospital, CHU Toulouse* *24 chemin de Pouvourville 31059 Toulouse France*
TITLE	***DUPECZEMAIN:*** *double blind placebo-controlled randomized multicenter study assessing the efficacy and safety of dupilumab in moderate to severe chronic hands eczema refractory to highly potent topical corticosteroids*
JUSTIFICATION/CONTEXT	*Chronic hand eczema (CHE) is a frequent chronic inflammatory skin disease which may have significant physical, psychological and social impact on daily activities, emotional and social life as well as work. In CHE, there is a close relationship between atopic dermatitis (AD) (that involves 70% of patients), sensitization to environmental antigens and irritant triggering factors. There are limited treatment options for CHE refractory to highly potent topical steroids. The only systemic treatment labelled in CHE, alitretinoin, is associated with moderate efficacy, high drop-out due to adverse events and it requires strict contraception measures in women of child bearing potential. Dupilumab has recently demonstrated high efficacy and good safety profile in the treatment of moderate-to-severe AD. There is a crucial need of developing new treatment options in CHE refractory to topical therapy. We hypothesise that Dupilumab will also have high efficacy and good safety profile in the treatment of moderate to severe CHE refractory to highly potent topical corticosteroids.*
PRIMARY OBJECTIVE	*To demonstrate that dupilumab is more effective than placebo for the treatment of patients with moderate-to-severe CHE who are resistant or intolerant to highly potent topical steroids.*
DESIGN OF THE STUDY	*Double-blind placebo-controlled randomised multicenter study*
INCLUSION CRITERIA	*- Adult Patients (≥18 years) affiliated to a social insurance protection regimen.* *- Patients with moderate to severe chronic (>6 months) hand eczema with an Investigator global assessment (IGA) of 3 or 4 (out of a scale of 0 to 4).* *- Patients intolerant or resistant to highly potent topical corticosteroids. Inadequate response to highly potent topical corticosteroids is defined as a history of failure to achieve and maintain remission or a low disease activity state (comparable to an IGA score of 0 [indicating clear] to 2 [indicating mild]) despite treatment with a daily regimen of highly potent topical corticosteroids applied for 14 days or for the maximum duration recommended for highly potent topical corticosteroids.* *- Patients who are able to understand the study procedures including the ability to complete patient-oriented questionnaires.* *- Patients who are able to apply a stable dose of emollients within 7 days before the baseline visit.* *- Patients who agree to sign the written informed consent.*

EXCLUSION CRITERIA	*- Hypersensitivity to dupilumab or to any of its ingredients* *- Patients under adult autonomy protection system* *- Any other condition (e;g., psoriasis) on the hands that according to the investigator will impair the ability to evaluate treatment effect.* *- Treatment with topical corticosteroids or topical calcineurin inhibitors within one week of baseline.* *- Treatment with oral immunosuppressants (including cyclosporine, methotrexate, azathioprine, mycophenolate mofetil), alitretinoin or phototherapy within 4 weeks of baseline visit.* *- Treatment with an investigational drug within 8 weeks (or 5 half-lives) of baseline.* *- Active chronic infection requiring the use of a systemic antibiotic within 2 weeks before study start.* *- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g., tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystis, aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections, per investigator judgment.* *- History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening.* *- Positive for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C antibody at the screening visit.* *- Patients with known helminth infections.* *- Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study. Women of childbearing potential who are sexually active and unwilling to use adequate birth control.*
STUDY TREATMENT/STRATEGIES/ PROCEDURES	*Patients will be randomised 1:1 to receive dupilumab 300 mg every other week after a 600 mg-loading dose of dupilumab on day 0 or placebo.* *The study consists in three phases: screening, treatment phase (16 weeks) and follow-up (4 weeks).*
JUDGEMENT CRITERIA	*Evolution of the mTLSS score (modified Total Lesion Symptom Score) at week 16 since baseline.*
SIZE OF THE STUDY	*Sample size calculations are based on a clinically meaningful absolute difference between groups in the mean percentage change in mTLSS score from baseline to Week 16 of -25% (greater percentage decrease expected in dupilumab compared with placebo). Assuming a standard deviation of 40% in both groups, sample size of 84 patients (42 by group) will achieve over 80% power to detect such a difference with a significance level (Type-I error) of 0.05 using a two-sided two-sample t-test.* *To account for potential non-evaluable patients estimated to 10%, a total of 94 patients will have to be randomised.*
NUMBER OF CENTRES PLANNED	*It is a multicenter national study performed in four expert centres in dermato-allergology, where physicians are used to manage patients with moderate to severe CHE.*
DURATION OF THE STUDY	*Duration of the inclusion period: 54 months.* *Duration of each patient's participation: 21 to 24 weeks.* *Total duration of the study: 60 months.*

STATISTICAL ANALYSIS OF THE DATA	*In primary efficacy analysis, the percentage change in mTLSS score from baseline to Week 16 will be compared between both groups using a covariance analysis including the group, the stratification factor (personal history of atopic dermatitis) and the baseline mTLSS score as covariables. Treatment effect will be tested at a 5% significance level (confirmatory test). The ITT population will be used for this primary efficacy analysis. Missing data on mTLSS score at Week 16 will be replaced using the Last-Observation-Carry-Forward (LOCF) imputation method.*
EXPECTED CONSEQUENCES	*The expected consequences of this study is that a 16-week course of dupilumab will be more effective than placebo for the treatment of moderate to severe CHE not adequately controlled with topical therapy.*

3. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION

3.1. CURRENT STATE OF KNOWLEDGE

3.1.1. OF THE PATHOLOGY

Hand eczema is a frequent chronic inflammatory skin disease with a 1-year prevalence of 7.5 to 9.5% of adults. It is estimated that about 5 to 10% of patients have severe hand eczema and 20% moderate hand eczema (1). Moderate to severe chronic hand eczema can represent a serious handicap for patients. It may be associated with pain, itching, bleeding and inability to work. Due to its chronicity and treatment resistance, hand eczema may have significant physical, psychological and social repercussions on daily, emotional, social and work and can sometimes result in loss of job and prolonged disability (2)(3) (4–6). In hairdressers, bakers and machine workers, up to 18% of patients had to change jobs due to hand eczema (7). The mean annual cost of the disease per patient varies from 1700 to 9700 euros, combining direct costs and indirect costs (8). A large amount of these costs is represented by the occupational costs with absenteeism and loss of work productivity. These are especially important in patients with severe hand eczema. It has been shown that 65% of patients with severe hand eczema reported loss of productivity at work, with an average of 10.1 days per patient per month (8). In summary moderate to severe forms of hand eczema may be associated with significant disease burden similar to moderate to severe forms of atopic dermatitis and psoriasis.

The etiology of hand eczema is multifactorial and the common pattern is characterized by chronic disruption of skin barrier. Environmental factors such as chronic exposure to irritants and allergens are often present. The disrupted skin barrier allows the penetration of allergens promoting the development of contact allergy. There are also genetic predisposing factors to hand eczema. Atopic dermatitis related genes regulating skin barrier structure and function such as *filaggrin (FLG)* are strong predisposing factors for hand eczema and more than 50% of patients with hand eczema have a history of atopy. Skin barrier related proteins such as filaggrin, filaggrin 2 and hornerin are down regulated in hand eczema patients as shown by proteomic analysis (9). There is a close relationship between atopic dermatitis, the sensitization to environmental antigens and the development of irritant dermatitis. In our cohort of patients with hand eczema, more than 70% of patients have a history of atopy and/or high IgE. In addition, it has been shown in experimental models that Th2 response are dominant in barrier-disrupted skin subsequently exposed to foreign antigens (10).

3.1.2. OF REFERENCE TREATMENTS/STRATEGIES/PROCEDURES AND THOSE BEING STUDIED

The management of hand eczema is based upon prevention and avoidance strategies using gloves, reducing exposure to irritants and regular use of emollients. Short courses of potent or super potent topical corticosteroids are recommended to control flares. There is limited evidence about the efficacy of topical calcineurin inhibitors in hand eczema with conflicting results from randomized clinical studies (2). The low penetration/permeation of topical agents through the skin of the hands explains the limited efficacy of topical anti-inflammatory agents. Most often, overnight occlusion should be advocated to allow for sufficient penetration of topical anti-inflammatory drugs. In the long-term, such measures are frequently unpractical and cumbersome for patients.

The treatment of patients with moderate to severe hand eczema resistant to topical therapy is difficult. Alitretinoin and phototherapy are recommended in patients with moderate to severe disease not adequately controlled with standard treatment. Phototherapy is of limited efficacy and its effects are mainly short lasting. Alitretinoin is a panagonist synthetic retinoid approved for the treatment of moderate to severe hand eczema (11). There has been a debate regarding the benefit/ risk of alitretinoin and the true effect on quality of life as summarized by NICE (12). Even if a certain proportion of patients (39%) achieved clear or almost clearance of hand eczema at 6 months with alitretinoin in a phase III pivotal study (13),drop out due to adverse events especially headache are common and the drug requires strict contraception measures in women of child bearing potential due to high teratogenic potential. According to the NICE guidelines, alitretinoin is recommended as a possible treatment for people with severe chronic hand eczema if: their eczema has not improved with treatments called potent topical corticosteroids **and** standard assessments show that their eczema is severe and is affecting their quality of life. Alitretinoin treatment should be stopped as soon as the eczema has clearly improved making it unsuitable for long-term use. Oral immunosuppressants such as methotrexate and cyclosporine are used off-label in refractory cases of hand eczema (14).

Epidemiological data show that similar to atopic dermatitis very few patients with moderate to severe chronic hand eczema (CHE) receive systemic treatment mainly due to the potential adverse reactions and the limited efficacy of systemic treatment (15).

Consequently, there is a need for new treatment options in patients with moderate to severe hand eczema who are not adequately controlled with topical therapy.

Dupilumab is a fully human monoclonal antibody directed against IL-4 receptor alpha, inhibiting signaling of IL-4 and IL-13. IL-4 and IL-13 are important cytokines driving Type 2 inflammatory responses and IgE class switching that are essential in atopic dermatitis and asthma as well as other type 2 inflammation mediated diseases. In addition, we have shown recently that IL-4 and Il-13 signaling blocks the production of epidermal proteins important for skin barrier protection such as filaggrin, hornerin and filaggrin-2 (16). Dupilumab has demonstrated robust and rapid efficacy as well as favorable safety profile in moderate to severe atopic dermatitis (AD) in phase III trials (17,18). About 40% of patients with moderate to severe atopic dermatitis are clear or almost clear of AD and between 50 and 70% achieve at least 75% improvement in the Eczema Area and Severity Index at 16 weeks with the labeled dose of dupilumab.
Dupilumab has been granted priority review by the Food and Drug Administration and has received approval for moderate to severe AD in adults in the USA in March 2017 and in Europe in September 2017. In addition, dupilumab is associated with a good safety profile (17, 18).

The rationale for the efficacy of dupilumab in hand eczema is based upon the following arguments:

- The close relationship between atopic dermatitis and hand eczema, both having on the hands the same clinical and histological presentation.
- The high frequency of an atopic background in patients with hand eczema: history of atopic dermatitis, presence of null mutations in the *filaggrin* gene, presence of atopic comorbidities, high IgE levels in serum.
- The ability of dupilumab to favorably influence skin barrier by blocking IL-4 and IL-13 which are important cytokines involved in the regulation of skin barrier genes transcription as shown in our laboratory work in atopic dermatitis(16).

In summary there are compelling arguments to hypothesize that dupilumab may be effective to clear hand eczema. Given the substantial evidence gathered regarding dose selection with dupilumab in atopic dermatitis and considering the close relationship between hand eczema and atopic dermatitis, the dose of dupilumab labelled by the FDA and EMA for use in atopic dermatitis (AD) will be tested in this study in hand eczema. Similarly, the treatment duration evaluated will be the 16-week treatment duration tested in phase III studies with dupilumab in AD.

3.2. THE HYPOTHESES OF THE STUDY AND RESULTS EXPECTED

- The primary hypothesis of the study is that a 16-week treatment with dupilumab is more effective than placebo to improve lesions and symptoms severity in moderate to severe hand eczema refractory to highly potent topical corticosteroids.
- The secondary hypotheses are that a 16-week treatment with dupilumab is more effective than placebo to improve patient pruritus and pain, quality of life, sleep loss, physician and patient global assessment of disease severity, work productivity and AD severity (if appropriate).Another secondary hypothesis is that 16 weeks treatment with dupilumab is a safe option compared to placebo.

3.3. REASONS FOR THE METHODOLOGY CHOICES

We will conduct a double-blind randomized placebo-controlled multicenter study evaluating the efficacy and safety of dupilumab for the treatment of moderate to severe hand eczema refractory to highly potent topical corticosteroids.

- Regarding the choice of the control group, the use of alitretinoin, the only approved systemic treatment of hand eczema, has not been pursued based on the following arguments:

  - Alitretinoin is associated with recognizable adverse reactions (headache) which make blinding difficult and could influence treatment evaluation

  - The high teratogenicity of alitretinoin

Taken these 2 points into consideration, the choice of a placebo-control design was chosen. This design is medically acceptable because hand eczema is a non-life threatening disease and a 16-week course of placebo will not generate permanent disability in patients. Moreover, epidemiological data show that, similar to atopic dermatitis, very few patients with moderate to severe chronic hand eczema receive systemic treatment mainly due to the potential adverse reactions and the limited efficacy of systemic treatment (15). Finally, we have to notice that according to these points, such design is commonly used for psoriasis, atopic dermatitis and hand eczema.

- The rationale for the dose selection is based on the robust phase III and registration data for dupilumab in atopic dermatitis, a disease which displays a close relationship with hand eczema.
- The rationale for the use of the mTLSS is based upon its relevance to hand dermatitis and the ability of this score to detect clinically relevant changes in disease severity as assessed by the main clinical signs and symptoms of hand eczema as demonstrated in several clinical trials programs

- The rationale for the 16-week treatment duration is based on the rapid onset of action of dupilumab in atopic dermatitis. The only drug approved for hand eczema, alitretinoin is a slow acting drug showing modest efficacy after 24 weeks (19). This is probably due to the intrinsic properties of retinoids known to be slow acting agents. The response of hand eczema to systemic immunomodulatory agents used in atopic dermatitis is rapid. As an example oral cyclosporine has shown efficacy in hand eczema in a 6-week randomized controlled trial (20).
- Randomisation will be stratified based on the presence of a personal history of atopic dermatitis as it is expected to be the major factor potentially influencing the primary end point. Baseline severity is not expected to influence the primary end-point as relative change in mTLSS is not expected to be influenced by disease severity.

3.4. BENEFIT/RISK RATIO

Dupilumab has been approved in the USA and in EU for use in moderate to severe atopic dermatitis when systemic treatment is indicated. The foreseeable benefits are clearance or almost clearance of hand eczema in about 40% of patients and 75% improvement in the severity score in 50 to 70% of patients at 16 weeks. The foreseeable risks are according to the dupilumab US label:

- Hypersensitivity (rare)
- The occurrence of eye related disorders (conjunctivitis, keratitis, blepharitis, eye pruritus)
- Oral herpes or other herpes simplex virus infection
- Injection site reactions
- Initial increase from baseline in eosinophil count

The anticipated benefit-risk ratio of dupilumab for the treatment of moderate to severe CHE appears to be highly favorable.

3.5. EXPECTED CONSEQUENCES

The expected consequences of this study is that a 16-week course of dupilumab is proven to be more effective than placebo for the treatment of moderate to severe hand eczema not adequately controlled with topical therapy. We hypothesize that the treatment effect with dupilumab is similar to the one in atopic dermatitis. In this case the study results would support consultation with regulatory authorities worldwide to plan for the development of a clinical trials program leading to potential regulatory approval of dupilumab for use in patients with moderate to severe hand eczema, addressing an important medical need.

4. OBJECTIVES OF THE STUDY

4.1. PRIMARY OBJECTIVE

The primary objective of the study is to demonstrate that dupilumab is more effective than placebo for the treatment of patients with moderate to severe chronic hand eczema (CHE) who are resistant or intolerant to highly potent topical corticosteroids as determined by the evolution at week 16 of the mTLSS since baseline.

4.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To demonstrate that dupilumab is more effective than placebo to improve pruritus induced by CHE at week 16 as compared to baseline.
- To demonstrate that dupilumab is more effective than placebo to improve pain induced by CHE at week16 as compared to baseline.
- To demonstrate that dupilumab is more effective than placebo to improve quality of life at week 16 as compared to baseline.
- To demonstrate that dupilumab is more effective than placebo to improve sleep loss induced by CHE at week 16 as compared to baseline.
- To demonstrate that dupilumab is more effective than placebo to induce clearance or almost clearance of CHE at week 16 as defined by the investigator and by the patient.
- To demonstrate that dupilumab is more effective than placebo to improve work productivity at week 16 as compared to baseline.
- To evaluate the efficacy of dupilumab on other parts of the body as compared to placebo, in the expected 50% of patients who have eczema not limited to the hand.
- To evaluate the safety of dupilumab as compared to placebo throughout the course of the study.
- To evaluate the evolution of laboratory parameters of patients receiving dupilumab compared to those receiving placebo.

5. CONCEPTION OF THE STUDY

5.1. THE DESIGN OF THE STUDY

This is a double-blind randomized placebo-controlled study evaluating the efficacy and safety of dupilumab for the treatment of moderate to severe hand eczema. Patients will be randomized 1:1 to receive dupilumab 300 mg every 2 weeks after a 600 mg-loading dose of dupilumab on day 0 or placebo.
The study consists in three phases: screening, treatment phase (16 weeks) and follow-up (4 weeks). It is a multicenter national study performed in ~~three~~ four expert centers of dermato-allergology that are used to manage patients with moderate to severe hand eczema.
The study will be a regional multicenter study in dermato-allergology expert centers in the South West region of France.

5.2. RANDOMISATION METHODS

Patients will be randomly assigned in a 1:1 ratio into the dupilumab or the placebo group using a computer-generated randomization sequence with permuted-blocks. The randomization will be stratified on the most important parameter potentially influencing outcome: the presence or not of a personal history of atopic dermatitis.
The randomization list will be established by an independent statistician at Toulouse hospital not involved in the trial before the start of the study.

Patients will be randomized on Day 0 visit by the investigators using the “randomization” web page of the eCRF after signatory of informed consent and eligibility criteria check. After validating the content, the site immediately communicates to the investigator and to the pharmacy the patient's unique randomization number in the study as result of the randomization.

A document describing the randomization procedure will be kept confidentially in the Biostatistic Unit (USMR du CHU de Toulouse).

6. ELIGIBILITY CRITERIA

6.1. INCLUSION CRITERIA

- Adult Patients (≥18 years) affiliated to a social insurance protection regimen.
- Patients with moderate to severe chronic (≥6 months) hand eczema with an Investigator global assessment (IGA) of 3 or 4 (out of a scale of 0 to 4).
- Patients intolerant (according to the physician) or resistant to highly potent topical corticosteroids. Inadequate response (resistance) to highly potent topical corticosteroids is defined as a history of failure to achieve and maintain remission or a low disease activity state (comparable to an IGA score of 0 [indicating clear] to 2 [indicating mild]) despite treatment with a daily regimen of highly potent topical corticosteroids applied for 14 days or for the maximum duration recommended for highly potent topical corticosteroids.
- Patients who are able to understand the study procedures including the ability to complete patient-oriented questionnaires.
- Patients who are able to apply a stable dose of emollients within 7 days before the baseline visit.
- Patients who agree to sign the written informed consent.

6.2 EXCLUSION CRITERIA

- Hypersensitivity to dupilumab or to any of its ingredients
- Patients under adult autonomy protection system
- Any other condition (e;g., psoriasis) on the hands that according to the investigator will impair the ability to evaluate treatment effect.
- Treatment with topical corticosteroids or topical calcineurin inhibitors within one week of baseline.
- Treatment with oral immunosuppressants (including cyclosporine, methotrexate, azathioprine, mycophenolate mofetil), alitretinoin or phototherapy within 4 weeks of baseline visit.
- Treatment with an investigational drug within 8 weeks (or 5 half-lives) of baseline.
- Active chronic infection requiring the use of a systemic antibiotic within 2 weeks before study start.
- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g., tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystis, aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections, per investigator judgment.
- History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening.
- Positive for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C antibody at the screening visit.
- Patients with known helminth infections.
- Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study. Women of childbearing potential who are sexually active and unwilling to use an adequate birth control method.

7.1. METHODS OF RECRUITMENT

Patients will be recruited from the outpatient dermatology and allergology clinics of the participating centers. The participating centers are tertiary care referral centers for patients with moderate to severe hand eczema. They have a dedicated dermato-allergology clinic and are able to select 2 to 3 patients who are potential candidates for the study each month.
The regional network of office and hospital based dermatologists from the participating regions will be contacted for organizing patients referral. In addition, the network of occupational physicians in the participating regions will be informed about the study.

8. STUDY TREATMENTS/STRATEGIES/PROCEDURES

8.1. TREATMENT/STRATEGY/PROCEDURE BEING STUDIED

Dupilumab 300 mg syringe (2 mL) or matching placebo for subcutaneous administration. Two injections of 300 mg dupilumab or matching placebo will be performed at day 0 followed by one injection of 300 mg or matching placebo every 2 weeks until week 14.

8.2.1. DISTRIBUTION AND MANAGEMENT OF MEDICINAL PRODUCTS

At the start of recruitment, enough kits will be sent to each site (buffer) to allow for initial treatment allocations in case several patients are recruited simultaneously, until the next shipment can arrive.
The Investigator, the hospital pharmacist, or dedicated personnel allowed to store and dispense the IMP (Investigational Medical Product) will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.
When the opening and the reglementation of the study will be sorted, the different pharmacies will be contacted to store two complete kits (each kit containing 10 syringes) according to the randomization list in order to have the complete treatment for 2 patients.
When a patient is randomized, the pharmacy of the center or the local study team will sent to the center pharmacy a prescription with the scheduled visit date. The pharmacy will deliver the treatment for one month to the patient and an order will be sent to the PCEC of Toulouse to get a subsequent kit for the next patient.
This will be sent by Toulouse to the center in the week following the order.
The subsequent dispensations to the clinical trial unit will be organised after the planification of each visit for a patient. This will be traced in the prescription form and the reception of IMP and its administration will be recorded in the tracability logs.

8.2.2. DISPENSING THE MEDICINAL PRODUCT

All IMPs will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allows the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

The Investigator or delegate will keep accurate records of the quantities of the IMP dispensed, used and unused by each patient.

Proper recording of treatment kit numbers will be done as required on appropriate electronic case report form (e-CRF) page for accounting purposes.

The Investigator (or designee) tracks treatment accountability/compliance, either by diary, or by counting the number of used and unused treatment kits and syringes and completes the appropriate page of the patient treatment log.
The monitor in charge of the study then checks the data entered on the IMP administration page (in e-CRF) by comparing them with the patient treatment log forms.
Dupilumab and placebo will be administered by subcutaneous injection by a dedicated nurse during dedicated visits. Therefore, compliance will be guaranteed.

8.2.3. STORAGE

All IMP should be stored in an appropriate, locked room under the responsibility of the Investigator or other authorized persons (eg, pharmacists) in accordance with local regulations, policies, and procedures.
Control of storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.
Dupilumab and placebo will be stored refrigerated at 2°C to 8°C in the original carton to protect from light.

8.2.4. RETURN AND DESTRUCTION OF UNUSED PRODUCTS

The destruction of all used and unused units provided by SARD will be the responsibility of the Sponsor who will manage the organization and all logistics related to this activity. The destruction of non-shipped and/or expired units remaining at SARD will be the responsibility of SARD who will manage the organization and all logistics related to this activity after obtaining a greenlight from the Sponsor.

The Sponsor is responsible for ensuring that adequate records are maintained regarding the accountability and traceability of the units delivered to investigational sites as required by and in accordance with applicable law, statutes and regulations. The Sponsor is responsible for ensuring that reconciliation is performed for all units delivered to investigational sites.

8.3. BLINDING

8.3.1. ORGANISATION OF BLINDING

Dupilumab and placebo will be provided in identically matching 2 mL pre-filled syringes. To protect the blind, each treatment kit of 2 mL (dupilumab/placebo) glass pre-filled syringes will be prepared such that the treatments (dupilumab and its matching placebo) are identical and indistinguishable and will be labeled with a treatment kit number. The treatment kit number list will be generated by SARD. This list gives the correspondence between the treatment numbers and the treatment arms (dupilumab or placebo). Both the patient and Investigator will be blinded to assigned active drug or placebo for the whole study period.

8.3.2. UNBLINDING

Investigators may request unblinding for a participant for safety purpose. These requests will be made to the pharmacy unit of the Toulouse Hospital. Each intentional break of the blind should be reported to the sponsor and documented in the patient's CRF.

The PCEC will provide blinding letters to the centers in order to allow for the emergency unblinding if necessary.

The sponsor's vigilance unit will also have the randomization list and the correspondence between the numbers and the content of syringes in case of required unblinding (for potential suspected unexpected serious adverse reaction (SUSAR) regulatory notification).

Treatment allocation will be provided at the end of the study for all subjects after last subject has completed the study, complete cleaning of database and statistical analysis plan validated.

9. ASSOCIATED TREATMENTS AND PROCEDURES

9.1. APPROVED ASSOCIATED TREATMENTS/PROCEDURES

Emollients are approved for use in patients during the course of the study. Patients are allowed to take anti-histamines if medically indicated during the study. Patients with comorbid asthma should be on stable treatment. Any change in the dosage of anti-histamines should be captured in the source documents and case report form.

9.2. PROHIBITED ASSOCIATED TREATMENTS/PROCEDURES

Some treatments/procedures are prohibited during the study as either they may influence disease outcome or may pose a safety risk for patients.
Treatment with the following concomitant medications is prohibited during the study
- Treatment with immunomodulating biologics
- Treatment with an investigational drug (other than dupilumab)
- Treatment with topical corticosteroids or topical calcineurin inhibitors; such agents should not be administered during the study.
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.), except if critically medically needed to treat concurrent medical conditions (e.g., asthma).

Study drug will be temporary discontinued (5 half-life before and after vaccination) if a treatment with live (attenuated) vaccine is used through week 16
In addition, major surgery procedure and phototherapy (medical device or tanning) are prohibited during the 16-week treatment period.

Rescue therapy: if a patient presents with a severe flare of CHE during the course of the study which cannot be managed with emollients and requires intervention, a unique rescue 2-week course of highly potent corticosteroid (betamethasone dipropionate cream) will be administered. The amount of drug used will be recorded. Study treatment will be unchanged.

9.3. OPTIONAL SUB-STUDY

Patients included in the investigation center of Lyon, it will be proposed to participate to an optional pathophysiology sub-study to understand the mechanism of action of dupilumab.
For patients who give their written consent after receiving oral and written adequate information, a 3mm dorsal hand skin biopsy samples will be obtained at inclusion and repeated 16 weeks after the treatment initiation. The baseline biopsy will be performed at the most affected site of the dorsal hand. The 16-week biopsy will be performed close (2mm) to the baseline biopsy. Biopsy samples will be transferred to the lab unit (UDEAR Inserm U1056, Toulouse Purpan Hospital) and digested; cell suspensions will be sorted using flow cytometry. Sorted cell types will be exposed to a lysis buffer and RNA will be extracted. Single-cell RNA sequencing will be performed as described elsewhere (Define Major Fibroblast Populations in Human Skin Q18, Tabib T et al JID 2017) on each sample to identify distinct cell populations and distinct RNA signature within a specific cell type.
RNA-Sequencing will facilitate the ability to look at alternative gene spliced transcripts, post-transcriptional modifications, gene fusion, mutations/SNPs and changes in gene expression under treatment. Skin biopsy may lead to a located bleeding which will be avoided or limited by the cutaneous suture. A cutaneous infection may happen after performing a skin biopsy. The complete healing is usually obtained in 10 to 14 days. A permanent scar will persist. Smoking patients may experience healing difficulties. The clinical aspect of the scar varies from a person to an other. The healing issues which can arise are mainly delays of healing, hypertrophic scars, depressed scars, or change of skin color.
The pain associated to the biopsy sampling will be released according to the usual methods of pain management for example by a level 1 analgesic.
The stitches will be removed at Visit 2 by the site staff.

A biological collection will be realized with residual material after analysis (cutaneous biopsy, extracted ARN) to perform additional analyses (confirmation of a result for example) if needed. Biologic samples will be retained at UDEAR Inserm U1056, Toulouse Purpan Hospital.
Blood sample will be collected (10 ml) at V1 and V9. 1 heparin blood collection tube (5 ml) and 1 SST tube (5 ml).
Based on the results obtained from skin biopsies, the blood collection will allow us to check for pro- or anti-inflammatory cytokines and neuropeptids in the serum and to perform transcriptomic Rnaseq analysis on circulating blood immune cells. These data will be complementary to those obtained from skin biopsy and should allow us to define a neuro-inflammatory signature in chronic hand eczema and to follow its evolution under treatment with dupilumab.
Blood samples will be identified and stored at theU1056 INSERM laboratory, UDEAR, Purpan Hospital, CHU de Toulouse (Dr Nicolas Gaudenzio).

10. JUDGEMENT CRITERIA

10.1. MAIN JUDGEMENT CRITERION

- The primary outcome measure will be the 16-week percent change since baseline of the severity score mTLSS (modified Total Lesion Symptom Score).
- The mTLSS combines an evaluation of hand eczema lesions severity including 6 key signs (erythema, desquamation, lichenification/hyperkeratosis, vesiculae, oedema, fissures) and the intensity of pruritus and pain.

10.2. SECONDARY JUDGEMENT CRITERIA

- Evolution of pruritus associated with CHE at week 16 since baseline measured with a visual analog scale.
- Evolution of pain associated with CHE at week 16 since baseline measured with a visual analog scale.
- Improvement of quality of life at week 16 since baseline measured by DLQI (Dermatology Life Quality Index) and EQ-5D.
- Evolution of sleep loss associated with CHE at week 16 since baseline measured with a visual analog scale.
- Clearance or almost clearance of hand eczema at week 16 as defined by an Investigator's global assessment (IGA) of 0 or 1.
- Clearance or almost clearance of hand eczema at week 16 as assessed by the Patient's global assessment (PaGa) of 0 or 1.
- Improvement of work productivity at week 16 since baseline as assessed by the WPAI questionnaire (Work Productivity and Activity Impairment).
- Evolution of the Eczema Area and Severity Index at week 16 since baseline in patients who have eczema on other parts of the body than the hands.
- The safety throughout the course of the study (at 20 weeks since baseline) by monitoring adverse events, serious adverse events, injection site reactions.
- The evolution of laboratory parameters (full blood count, total IgE and specific IgE) at week 16 since baseline.

11. STUDY PROCEDURE

11.1. STUDY CALENDAR

The duration of the study for each patient will be between 21 and 24 weeks and will comprise three phases :

- A screening phase with a duration of 1 to 4 weeks
- A treatment phase with a duration of 16 weeks (4 treatment visits with injection, 4 self-injection at home or 4 injections at site by study staff and end of treatment visit)
- A post treatment follow-up phase with a duration of 4 weeks (follow up visit planned 6 weeks after the last injection and 4 weeks after the end of treatment visit)

The inclusion of the first patient happened in July 2019. The inclusion period is 54 months.

11.2. TABLE SUMMARISING PATIENT FOLLOW-UP

Phase	**Screening**	**Treatment period**									**Follow up period**
Visit	**Screening**	**V1**	**(V2)**	**V3**	**(V4)**	**V5**	**(V6)**	**V7**	**(V8)**	**V9**	**V10 FU Visit**
Day/Week	Up to 4 weeks prior to Visit 1	Day 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3
Informed consent	X										
Height and weight		X								X	
Demographics and characterisation of hand eczema	(X)	X									
Previous therapy for hand eczema	(X)	X									
In-/exclusion criteria	X										
Concurrent diagnoses	(X)	X									
Medical history	(X)	X									
Duration of hand eczema and other locations of eczema	(X)	X									
Other atopic comorbidities	(X)	X									
Concomitant medication	(X)	X		X		X		X		X	X
Physical examination	(X)	X									
Randomization		X									
Adverse Event(s)		X		X		X		X		X	X
AESI (Conjunctivitis)		X		X		X		X		X	X

Phase	**Screening**	**Treatment period**									**Follow up period**
Visit	**Screening**	**V1**	**(V2)**	**V3**	**(V4)**	**V5**	**(V6)**	**V7**	**(V8)**	**V9**	**V10 FU Visit**
Day/Week	Up to 4 weeks prior to Visit 1	Day 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3
Laboratory – Biochemistry (fasting)		X								X	
Laboratory full blood count	X									X	
Laboratory screening for hepatitis B, C and HIV	X										
Laboratory including specific IgE dosage (only Toulouse site)		X								X	
Laboratory including Total IgE dosage		X								X	
Pregnancy test*	X	X		X		X		X		X	X
Vital signs (BP, pulse, temperature)		X									
Photographs		X				X				X	

Phase	**Screening**	**Treatment period**									**Follow up period**
Visit	**Screening**	**V1**	**(V2)**	**V3**	**(V4)**	**V5**	**(V6)**	**V7**	**(V8)**	**V9**	**V10 FU Visit**
Day/Week	Up to 4 weeks prior to Visit 1	Day 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3
Patients Global Assessment of disease severity		X		X		X		X		X	
Investigator´s Global Assessment of disease severity		X		X		X		X		X	
EASI		X		X		X		X		X	
mTLSS		X		X		X		X		X	
Hand eczema pruritus by VAS		X		X		X		X		X	
Hand eczema Sleep loss by VAS		X		X		X		X		X	
Hand eczema Pain assessment by VAS		X		X		X		X		X	
DLQI		X		X		X		X		X	
EQ-5D-5L		X		X		X		X		X	
WPAI		X								X	
Skin Biopsy (sub study only)		X								X	
Removal of the stitches (sub study only)			X								
Blood sample for sub study		X								X	
Subject treatment instructions		X									
Study treatment administration		X	(X)	X	(X)	X	(X)	X	(X)		

*Serum pregnancy test required at Screening visit and V9, urinary pregnancy test will be performed at V1, V3, 5, 7 and 10

Each visit will be conducted by the investigator (Dermatologist, Allergologist) at the dermatology outpatient clinic in the participating centers.

11.3. SCREENING VISIT

The screening visit is conducted by the physician investigator. The screening visit will occur between 1 week and at the latest 4weeks before the inclusion visit. A screening assessment to determine study eligibility will be performed at this visit. Before any examination related to the study, the investigator will obtain the patient's informed, written and freely given consent (or if necessary that of his legal representative)

OBTAINING CONSENT

During the screening visit, the investigator provides the patient with information and answers all his or her questions about the objective, the nature of constraints, foreseeable risks and benefits expected from the study. He also explains the patient's rights in relation to a biomedical research study and checks his eligibility criteria. A copy of the Patient Information and Informed Consent form is then given to the patient by the investigator.

After this information meeting, the patient has a period of time to consider his decision. The investigating doctor is responsible for obtaining the patient's written informed consent. The consent form must be signed BEFORE ANY CLINICAL OR LABORATORY EXAMINATION NEEDED FOR THE STUDY IS PERFORMED.

If the patient agrees to participate, he and the investigator clearly write their last names and first names, date and sign the consent form.

The various copies of the Patient Information and Informed Consent form are then distributed as follows:

- A copy of the Patient Information and signed Informed Consent form is given to the patient.
- The original copy is kept by the investigating doctor (even if the patient moves house during the period of the study) in a safe place inaccessible to third parties.
- At the end of inclusions or at the latest at the end of the study, a copy of each Informed Consent form is sent to the sponsor or his representative using the methods communicated in due course to the investigators.

DEMOGRAPHICS AND CHARACTERISATION OF HAND ECZEMA

At this visit, characterization of hand eczema will be performed by the physician investigator including, occupation, personal history of atopic dermatitis (as defined by Williams Criteria : Williams HC, Burney PG, Pembroke AC, Hay RJ. Validation of the U.K. diagnostic criteria for atopic dermatitis in a population setting. U.K. Diagnostic Criteria for Atopic Dermatitis Working Party. Br J Dermatol 1996;135:12-7.), presence of atopic comorbidities including asthma, allergic rhinitis and allergic conjunctivitis.

Duration of hand eczema, presence and evaluation of eczema on other sites of the body will be recorded.

Previous therapy received for hand eczema (medication, duration of exposure) will be recorded.

LABORATORY TESTING

Bloods sample will be drawn for safety and IgE follow up. The total volume of blood for the study will not exceed 50 ml.

At screening visit will performed:

- Full blood count including Eosinophils (EDTA tube 3ml) will be performed by site.
- Serum hCG – for women of child-bearing potential (tube SST 3ml): a serum pregnancy test must be taken at the screening visit in female subjects of child-bearing potential. This test will be performed by site.
- Screening for hepatitis B, hepatitis C and HIV (2 SST tubes de 7 ml) will be performed by site. It includes hepatitis B virus surface antigen, virus surface antibody, and virus core antibody, hepatitis C virus antibody, HIV-1 and HIV-2 antibody.

11.4. BASELINE VISIT (V1)

At the inclusion visit V1 at day 0, the following procedures will be conducted by the investigator or designee:

RANDOMIZATION PROCEDURE

The investigator completes the "randomization" web page after previously confirming all the eligibility criteria of the patient on the site. After validating the content (and particularly, randomization stratification factors), inclusion takes place and the site immediately communicates to the investigator and to the pharmacy the patient's unique number in the study, the result of the randomization, in particular the number of the treatment box.

DEMOGRAPHICS AND CHARACTERISATION OF HAND ECZEMA

At this visit, characterization of hand eczema will be performed by the physician investigator including, occupation (aggravating factors due to work environment), aggravating domestic factors, personal history of atopy including atopic dermatitis (as defined by Williams Criteria : Williams HC, Burney PG, Pembroke AC, Hay RJ. Validation of the U.K. diagnostic criteria for atopic dermatitis in a population setting. U.K. Diagnostic Criteria for Atopic Dermatitis Working Party. Br J Dermatol 1996;135:12-7.), history of patch testing with results, history of prick tests with results, and food allergy.

LABORATORY TESTING

- Serum Chemistry (heparin tube 5 ml) will be performed by site. It includes: sodium, potassium, creatinine, urea mitogen, calcium, alkaline phosphatase, aspartate aminotransferase, GGT, alanine aminotransferase, bilirubin, lactate dehydrogenase, cholesterol, LDL, HDL, triglycerides, glucose (fasting) albumin, protein.
- Total IgE will be performed by site
- Specific IgE (SST tube 3ml) will be performed for patients from Toulouse and Lyon sites, by the immunology laboratory Rangueil Hospital TSA50032, 1 av. du Pr. Poulhes, 31059 Toulouse Cedex, France.
- Urinary pregnancy test must be performed at baseline prior to randomization in female subjects of child-bearing potential.

WEIGHT AND HEIGHT

The subject height must be measured (without shoes) and weight must be determined (in indoor clothing and without shoes)

CONCOMITANT MEDICATIONS / ADVERSE EVENT (AE)

Any medication or vaccine that subject receives from 3 months priori screening through safety follow up must be recorded in the subject's medical record and the eCRF along with the details such as: reason for use, dates of administration (start and stop date), dosage information (dose and frequency). Similarly, concomitant procedures must also be recorded in the subject's medical record and the eCRF.

AEs must be collected from time of first trial-related activity after the subject has signed the informed consent form until completion of the clinical trial. AEs must be assessed by medically qualified personnel. AEs reported by the subject or observed by the investigator must be recorded on the AE form of the CRF and should be described.

AESI (Conjunctivitis) must be recorded in the eCRF and reported immediately to the Sponsor (see.section 10.3).

VITAL SIGNS

Vital signs (resting blood pressure, pulse and body temperature) must be assessed according to the flowchart before randomization.Vital signs also should be done at 1 hour post-injection (+/- 10 minutes) at baseline visit.

Vital signs will be measured in sitting position following at least 5 minutes rest.

Clinically significant abnormal vital signs at the baseline visit will be documented as medical history in the eCRF. It will be up to the investigator's discretion if the subject should be randomized into the trial. If an abnormal vital signs at any other visit than baseline visit is considered by the investigator to be clinically significant, it will be reported as an AE in accordance with the principles for data entry.

In case of abnormal findings, the vital sign measurement can be repeated approximately 15 minutes later with the subjects resting in a sitting position to verify the first measurement.

PHOTOGRAPHS OF THE HANDS: photographs of palms and dorsal hands will be performed. The trial sites will use their own equipment to take the photographs. Instruction for photography will be provided to the site in a photography procedure. The photographs will have no other subject identifier than the subject ID and will be collected by CRA on USB device. Sponsor may at its discretion use the photographs in publications, posters and similar types of information material.

PHYSICAL EXAMINATION AND INVESTIGATOR ASSESSMENTS

- Modified TLSS (21, 22): The seven individual CHE symptoms; (erythema, scaling, lichenification or hyperkeratosis, vesiculation, edema, fissures, and pruritus/pain) form the composite scale of mTLSS' strength and each one of them scores from 0 (mild) to 3 (severe). The scores are summed, extending from a base estimation of 0 (no signs or symptoms) to the most extreme of 21 (more serious disease).

Symptoms	**Severity, morphological description**
erythema	□ 0 = none □ 1 = mild erythema □ 2 = redness □ 3 = deep/dark red erythema
scaling	□ 0 = none □ 1 = mild fines scales, limited area □ 2 = thicker scales, extended area □ 3 = thick scales on more than 30% of the hand
lichenification	□ 0 = none □ 1 = mild thickening, limited area □ 2 = moderate thickening, extended area □ 3 = severe thickening, extended area
Skin vesicles	□ 0 = none □ 1 = vesicles on less than 10% of the hand □ 2 = vesicles on 10 to 30% of the hand □ 3 = vesicle on more than 30% of the hand
oedema	□ 0 = none □ 1 = mild oedema, on less than 10% of the hand □ 2 = oedema on more than 10% of the hand □ 3 = oedema and induration on extended area
cracking	□ 0 = none □ 1 = craking on a small part of the hand □ 2 = painful craking on multiple hand area □ 3 = deep/dark red erythema
Pruritus / pain	□ 0 = none □ 1 = mild discomfort several times a day □ 2 = recurring discomfort during the day □ 3 = persistent discomfort leading to sleep disorder

- Investigator's Global Assessment (IGA): IGA is a global assessment of the patient's overall severity of their CHE, based on a static, numeric 5-point scale from 0 (clear skin) to 4 (severe disease). The score is based on an overall assessment of the degree of erythema, papulation/induration, oozing/crusting, and lichenification. The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at previous visit.

Investigator's Global Assessment

Score	Disease severity	Standard IGA Scale	IGA morphological descriptors
0	Clear	No inflammatory signs of CHE	No erythema and no elevation (papulation/infiltration)
1	Almost clear	Just perceptible erythema and just perceptible papulation/infiltration	Barely perceptible erythema and/or minimal lesion elevation (papulation/infiltration) that is not widespread
2	Mild disease	Mild erythema and mild papulation/infiltration	Visibly detectable, light pink erythema and very slight elevation (papulation/infiltration)
3	Moderate disease	Moderate erythema and moderate papulation/infiltration	Dull red, clearly distinguishable erythema and clearly perceptible but not extensive elevation (papulation/infiltration)
4	Severe disease	Severe erythema and severe papulation/infiltration	Deep/dark red erythema, marked and extensive elevation (papulation/infiltration)

- EASI: The EASI assesses extent of disease at 4 body regions and measures 4 clinical signs: (1) erythema, (2) induration/papulation, (3) excoriation, and (4) lichenification each on a scale of 0 to 3. The EASI confers a maximum score of 72. The EASI evaluates 2 dimensions of AD:disease extent and clinical signs (23). To be performed only if CHE is associated with AD.

Calculation of the EASI

Body region	Erythema	Induration/ papulation	Excoriation	Lichenification	Area score	Weighting factor	Score
Head/neck	SS	SS	SS	SS	x AS	x 0.1	
Trunk	SS	SS	SS	SS	x AS	x 0.3	
Upper extremities	SS	SS	SS	SS	x AS	x 0.2	
Lower extremities	SS	SS	SS	SS	x AS	x 0.4	
The EASI score is the sum of the 4 body region scores							Range 0-72

AS: area score; EASI: Eczema Area and Severity Index; SS: Severity Score

EASI severity score scale and area score scale

Severity score scale	
0	None/absent
1	Mild
2	Moderate
3	Severe

Area score scale	
0	0% affected area
1	1% to 9% affected area
2	10% to 29% affected area
3	30% to 49% affected area
4	50% to 69 affected area
5	70% to 89% affected area
6	90% to 100% affected area

PATIENT QUESTIONNAIRES

- Patient's Global Assessment (PGA): The PGA is a single-item question asking the patient how they would rate their overall CHE symptoms over the past 24 hours. The 5 categories of responses range from "no symptoms"(0) to "severe."(4)

- DLQI: The Dermatology Life Quality Index (DLQI) is a simple, patient-administered, 10-item, validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the "last week." Response categories include "not at all," "a lot," and "very much," with corresponding scores of 1, 2, and 3, respectively, and unanswered ("not relevant") responses scored as 0. Scores range from 0-30 with higher scores indicating greater impairment of quality of life. A DLQI total score of 0 to 1 is considered as having no effect on a patient's health-related QoL (24), and a 4-point change from baseline is considered as the minimal clinically important difference threshold (25; 26).

- EQ-5D-5L: The European Quality of Life–5 Dimensions–5 Levels (EQ-5D-5L) is a standardized measure of health status that provides a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of 2 components: a descriptive system of the respondent's health and a rating of his or her current health state using a 0 to 100 mm VAS. The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his or her health state by ticking (or placing a cross) in the box associated with the most appropriate statement in each of the 5 dimensions. It should be noted that the numerals 1 to 5 have no arithmetic properties and should not be used as an ordinal score. The VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labeled "best imaginable health state" and "worst imaginable health state." This information can be used as a quantitative measure of health outcome. The EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single summary index by applying a formula that essentially attaches values (also called weights) to each of the levels in each dimension (27)

- Hand eczema Pruritus VAS: The hand eczema pruritus VAS is a patient administered single item scale designed to measure current pruritus from CHE using a 100 mm horizontal VAS. Overall severity of a patient's pruritus from CHE is indicated by placing a single mark on the horizontal scale (0 = none; 100 = as severe as you can imagine)

- hand eczema Pain VAS: The hand eczema pain VAS is a patient administered single item scale designed to measure current pain from CHE using a 100 mm horizontal VAS. Overall severity of a patient's pain from CHE is indicated by placing a single mark on the horizontal scale (0 = none; 100 = as severe as you can imagine)

- hand eczema Sleep loss VAS: The hand eczema sleep loss VAS is a patient administered single item scale designed to measure current sleep loss from CHE using a 100 mm horizontal VAS. Overall severity of a patient's sleep loss from CHE is indicated by placing a single mark on the horizontal scale (0 = no sleep loss; 100 = as severe as you can imagine).

- WPAI questionnaire: The work productivity and activity impairment questionnaire-atopic dermatitis (WPAI) records impairment due to CHE during the past 7 days. The WPAI-AD consists of 6 items grouped into 4 domains: absenteeism (work time missed), presenteeism (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment/absenteeism plus presenteeism), and activity impairment. Scores are calculated as impairment percentages (28), with higher scores indicating greater impairment and less productivity.

- Perform randomization (for details see page 30) and give subject treatment instructions to the patient
- Administer study drug (sub cutaneous injection of the first dose of dupilumab or placebo) : site staff will perform the first injection and will explain to patient how to perform self-injection and will stay with him for the first self injection (second injection)
- Monitor the patient for 1 hour after the SC injection: vital signs and AE assessment (for details see page 30) should be done at 1 hour post-injection (+/- 10 minutes). Injection site reaction (ISR) photograph will be taken, if applicable.

11.5. TREATMENT PERIOD

Treatment visits (n = 8) will be at week 2 (visit 2) and every 2 weeks until week 16 (visit 9). A follow-up visit will be performed at week 20. Visits will be organised in the outpatient clinic preferably with the same physician investigator in collaboration with a study nurse for investigational drug administration. The duration of the visits will be of 30 to 45 minutes. All appointments will be planified at day 0 and the patient will be provided with a full study schedule.

At study treatment stop (as per protocol or in case of premature stop), Asthmatic patients must be closely monitored: the investigator will assess the asthma and will decide to direct the patient to his pulmonologist if necessary. The patient will be informed about the necessity of consulting quickly in case of recurrence of asthmatic symptoms and as a matter of urgency in case of asthma crisis.

At each visit, in case of persistent conjunctivitis, not recovered with standard treatments, investigator will send the patient to a referent ophthalmologist of his establishment.

Visit 2/ Week 2:

The treatment allocated (dupilumab or placebo) will be administered at home (self_injection) or at site (by site staff) according to patient's preference.

Visit 3/ Week 4:

The following information will be collected:

- Concomitant medications and procedures
- AEs and AESI (Conjunctivitis)

The following procedures/assessments will be conducted by the investigator or designee:

- mTLSS,
- EASI (if applicable)
- IGA,
- PGA,
- DLQI,
- EQ-5D,
- Hand eczema Pruritus VAS,
- Hand eczema Pain VAS,
- Hand eczema Sleep loss VAS.

The treatment allocated (dupilumab or placebo) will be administered.

Visit 4/ Week 6:

The treatment allocated (dupilumab or placebo) will be administered at home (self_injection) or at site (by site staff) according to patient's preference.

Visit 5/Week 8:

The following informations will be collected:

- Concomitant medications and procedures
- AEs and AESI (Conjunctivitis)

The following procedures/assessments will be conducted by the investigator or designee:

- mTLSS,
- EASI (if applicable)
- IGA,
- PGA,
- DLQI,
- EQ-5D,
- Hand eczema Pruritus VAS,
- Hand eczema Pain VAS,
- Hand eczema Sleep loss VAS,
- Photographs of the hands,
- Urinary pregnancy test if applicable.

The treatment allocated (dupilumab or placebo) will be administered.

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Visit 6/ Week 10:

The treatment allocated (dupilumab or placebo) will be administered at home (self_injection) or at site (by site staff) according to patient's preference.

Visit 7/Week 12:

The following informations will be collected:

- Concomitant medications and procedures
- AEs and AESI (Conjunctivitis)

The following procedures/assessments will be conducted by the investigator or designee:

- mTLSS,
- EASI (if applicable)
- IGA,
- PGA,
- DLQI
- EQ-5D-5L
- Hand eczema Pruritus VAS,
- Hand eczema Pain VAS,
- Hand eczema Sleep loss VAS,
- Urinary pregnancy test (if applicable).

The treatment allocated (dupilumab or placebo) will be administered.

Visit 8/Week 14:

The treatment allocated (dupilumab or placebo) will be administered at home (self_injection) or at site (by site staff) according to patient's preference.

Visit 9/ Week 16:

The following information will be collected:

- Concomitant medications and procedures
- AEs and AESI (Conjunctivitis)

The following procedures/assessments will be conducted by the investigator or designee:
- mTLSS,
- IGA,
- EASI if applicable,
- PGA,
- DLQI,
- EQ-5D-5L,
- Hand eczema Pruritus VAS,
- Hand eczema Pain VAS,
- Hand eczema Sleep loss VAS,
- WPAI questionnaire,
- Photographs of the hands,
- Laboratory samples:
    - o Full blood count including Eosinophils
    - o Serum Chemistry
    - o Serum hCG – for women of child-bearing potential
    - o Total IgE
    - o Specific IgE

Asthma will be assessed for concerned patient. The investigator will decide to direct the patient to his pulmonologist if necessary.

11.6. FOLLOW UP VISIT (END OF STUDY VISIT)

Follow up visit will take place at week 20. It will consist in:
- collecting concomitant medications
- collecting adverse events and AESI (Conjunctivitis)
- Urinary pregnancy test if applicable.

Asthma will be assessed for concerned patient. The investigator will decide to direct the patient to his pulmonologist if necessary.

11.7. RULES FOR INTERRUPTING THE STUDY

The end of the study does correspond to the end of study participation.
In line with the current regulation, each patient can at any time withdraw from the study. The participation to this study is voluntary. The patient does not have to provide with any justification for withdrawing his/her participation. If a patient stops the treatment during the study, if he wants, he'll be followed in the study.
The investigator will have to complete an early termination visit sheet in the CRF indicating the reason for interruption of the study: premature discontinuation (efficacy/safety issue), lost to follow-up, withdrawal of consent, major deviation from the protocol.
The subject withdrawing prematurely from the study will not be replaced.

11.8. CONSTRAINTS RELATING TO THE STUDY

Patients included in this study can not participate simultaneously in another investigational drug study for the entire study duration. Participation of patients is voluntary and no monetary compensation will be provided.

11.9. COLLECTION OF BIOLOGICAL SAMPLES

Patients included in the centers of Lyon and Toulouse will be proposed to participate to an optional pathophysiology sub-study to understand the mechanism of action of dupilumab. For this sub-story,

A biological collection will be realized with residual material after analysis (cutaneous biopsy, extracted ARN) to perform additional analyses (confirmation of a result for example) if needed. Biologic samples will be retained at UDEAR Inserm U1056, Toulouse Purpan Hospital .

12. MANAGEMENT OF ADVERSE EVENTS AND NEW FACTS

12.1. DEFINITIONS

Adverse Event (Article R1123-46 of the Public Health Code)
Any harmful manifestation occurring in a participant in a research study that involves the human person, whether or not the event is related to the research or product to which the research relates.

Adverse reaction (Article R1123-46 of the Public Health Code)
Any adverse event occurring in a participant in a research study that involves the human person, when this event is related to the research or product to which the research relates.

Serious adverse reaction or event (Article R1123-46 of the Public Health Code and ICH-E2B guideline)
Any adverse reaction or event that:

- ✓ results in death,
- ✓ endangers the life of the participant,
- ✓ requires hospitalisation or prolongation of hospitalisation,
- ✓ causes an inability or significant or long-term disability,
- ✓ results in an abnormality or congenital malformation,
- ✓ or any event considered to be medically serious,

and with respect to the drug, regardless of the dose administered.

The expression “life-threatening" is reserved for an immediate life threat at the time of the adverse event.

Unexpected adverse reaction (Article R1123-46 of the Public Health Code)

- Any adverse reaction to the product including the nature, severity, frequency or outcome of which is inconsistent with the safety reference information referred to in the Summary of Product Characteristics or in the investigator’s brochure when the product is not authorised. In this protocol, the safety reference information is represented by IB v.12 (4-Apr-2018).

New fact (Article R1123-46 of the Public Health Code)

- Any new data that may lead to a reassessment of the risk to benefit ratio of the research or of the product being researched, changes in the use of this product, in the conduct of the research, or to the documents relating to the research, or data that may lead to the suspension, discontinuation or modification of the research protocol or similar research.

Intensity/severity : the table below will be used for AE severity grading.

Severity	Description
GRADE 1 – Mild	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
GRADE 2 – Moderate	Mild to moderate limitation in activity—some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3 – Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required hospitalizations possible.
GRADE 4 – Life-threatening	Extreme limitation in activity, significant assistance required; life-threatening (immediate risk of death); significant medical intervention/therapy required, hospitalization or hospice care probable.
GRADE 5 – Fatal	Death

12.2. DESCRIPTION OF EXPECTED SERIOUS ADVERSE EVENTS

The serious adverse events expected in the context of this protocol are listed here:

- related to the study treatment (dupilumab): rare hypersensitivity reaction, eyes disorders (severe conjunctivitis or keratitis for example), injection site reaction, herpes infection, hypereosinophilia. Other expected adverse events related to dupilumab are described in reference document (IB v.12 (4-Apr-2018)).
- related to the study procedures (blood tests, questionnaires) : none

related to evolution of the disease: relapse, flair of hands eczema

- related to skin biopsy (performed in optional sub-study) : skin biopsy may lead to pain, edema, located bleeding, cutaneous infection or healing issue (healing delay, persisting scar…).

Any serious adverse reaction reported in this study will be considered as "unexpected" (SUSAR) if it is not listed in section 10.2 of the protocol or in IB v.12 (4-Apr-2018) of dupilumab.

12.3. ACTION TO BE TAKEN IN THE CASE OF AN ADVERSE EVENT OR NEW FACT

Adverse events collection :

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.
All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms. All AEs must be recorded in the participant's medical record, stating the duration of the event, action taken by the investigator and outcome of the event. The investigator must evaluate the causal relationship between the study drug and the AE.

Exception to collection:
The following circumstances will not be collected:

- *admission for social or administrative reasons,*
- *hospitalisation predefined by the protocol,*
- *hospitalisation for scheduled medical or surgical treatment prior to the research,*

Adverse events of special interest

Conjunctivitis will be considered as adverse events of special interest (AESIs) in this trial and must be reported as serious adverse events even if there is no seriousness criteria.

It will require additional details to be recorded in the eCRF. Sponsor may request that the investigator forward complementary information, as appropriate.

Serious adverse events notification :

The investigator must immediately notify the sponsor on the day that he becomes aware of it of any serious adverse event or any new fact or pregnancy, if it occurs:

- after the date of signature of the consent form,
- at any time during the period of follow-up planned by the study for the participant,

If the investigator becomes aware of a serious adverse event, which he/she suspects is causally related to the research, occurring after the end of the clinical trial in a participant he/she has treated, he/she shall inform the sponsor without delay.

TYPE OF EVENT	NOTIFICATION METHOD	TIME LIMIT FOR NOTIFYING THE SPONSOR
Non-serious AE	In the case report form	No immediate notification
AE of special interest (conjunctivitis)	In the case report form + initial SAE declaration form	**Sponsor to be notified immediately**
SAE	Initial SAE declaration form + written report if necessary	**Sponsor to be notified immediately**
New fact	Declaration form + written report if necessary	**Sponsor to be notified immediately**
Pregnancy	Pregnancy declaration form	On confirmation of the pregnancy

Name of sponsor/Vigilance Unit : CHU de Toulouse
Dr Pascale OLIVIER-ABBAL
Fax: 05 61 77 84 11
E-mail: **vigilance.essaiscliniques@chu-toulouse.fr**

All these events must be monitored until they are **completely resolved**. The investigator will send the sponsor additional information (additional declaration form) concerning the evolution of the event not mentioned in the initial report.

The investigator and the sponsor must evaluate the causal relationship between the study drugs (dupilumab/placebo) and the SAE, independently. If the SAE is not related to the study drug, the investigator and the sponsor must determine the alternative causality (eczema, concomitant treatment, other pre-existing disease, etc…). If they are not agreed about the final causality assessment, this discrepancy has to be notified in the SAE report.

All SAE that are considered to be reasonably related to the IMP, will be defined as a "serious suspected adverse reaction".

Pregnancies

Pregnancy occurring during the period or immediately after a study does not constitute an SAE. However, a pregnancy must be notified in the same way as an SAE because it requires particular monitoring throughout its duration. In the event of pregnancy, dupilumab should be immediately discontinued and the pregnancy must be reported immediately of the Investigator's knowledge of it by fax to the Sponsor using the Pregnancy Reporting Form.
The Investigator will follow the female subject until completion of the pregnancy, and must notify the Sponsor of the outcome of the pregnancy immediately when having knowledge of the outcome using the Follow-Up Pregnancy Reporting Form.
Any anomaly observed in the foetus or child will then be notified. Any elective termination of pregnancy (ETP), medical termination of pregnancy (MTP) or spontaneous abortion must give rise to a notification of pregnancy, and if it necessitated hospitalisation, it must be passed on in the same manner as an SAE.

12.4. DECLARATION AND RECORDING OF UNEXPECTED SERIOUS ADVERSE REACTIONS AND NEW FACTS

The sponsor/vigilance unit immediately declares any **SUSAR** occurring during the study:
- to ANSM [the French Agency for the Safety of Health Products],

In addition, the sponsor/vigilance unit will record all SUSAR in the EudraVigilance database.

In the event of blinded research, the sponsor declares any SUSAR after unblinding.

The sponsor/ vigilance unit shall declare without delay **new facts** that have arisen during the research to:

- the ANSM,
- the Committee for the Protection of Persons,

The sponsor and the investigator will take the appropriate urgent measures. The sponsor will inform the competent authority and the committee for the protection of persons.

Summary table of declarations by type of study

Type of study and type of AE	Declaration to		Initial declaration period	Follow-up period
	Competent authority (EMA, ANSM, etc.)	CPP		
Drug: SUSAR	X		- death or life-threatening: without delay - other criteria: max. 15 days	Max. 8 days

12.5. ANNUAL SAFETY REPORT

Article R1123-61 of the Public Health Code)

For category 1 research, on the anniversary date of the *research authorisation* the sponsor will write a safety report (or Development Safety Update Report – DSUR) including:

- the list of serious adverse reactions that may be related to the experimental treatment(s) of the research, including expected and unexpected serious reactions, that occurred in the relevant study during the reporting period,
- a concise and critical analysis of the safety of the research participants.
- summary tables of all serious adverse reactions that have occurred in the study since the beginning of the research.

This report is sent to the ANSM and the CPP within 60 days of the anniversary date of *the research authorisation.*

13. STATISTICAL CONSIDERATIONS

13.1. SAMPLE SIZE OF THE STUDY

In this trial, patients will be randomly allocated to the two groups with a 1:1 ratio. Randomisation will be stratified based on the presence of a personal history of atopy atopic dermatitis.
For analysis of primary outcome, the percentage change in mTLSS score from baseline to Week 16 will be compared between both groups.

Sample size calculations are based on a clinically meaningful absolute difference between groups in the mean percentage change in mTLSS score from baseline to Week 16 of -25% (greater percentage decrease expected in dupilumab compared with placebo). Assuming a standard deviation of 40% in both groups, sample size of 84 patients (42 by group) will achieve over 80% power to detect such a difference with a significance level (type-I error) of 0.05 using a two-sided two-sample t-test (13).
To account for potential non-evaluable patients estimated to 10%, a total of 94 patients will have to be randomised.

Sample size computations were done using PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.

13.2. STATISTICAL ANALYSIS PLAN

A statistical analysis plan (SAP) will be issued and validated by the scientific committee of the study prior to the unblinding of the database. All statistical analyses detailed in the SAP will be conducted by a sponsor statistician using Stata® Version 11.2 or later or SAS® Version 9.3 or later. A single statistical analysis will be conducted at the end of the study.

13.3. SUBJECT POPULATIONS FOR ANALYSIS

- The Intention-to-Treat (ITT) population will consist of all randomized patients, independently of whether they receive study treatment or not. Patients will be analysed according to the treatment they were randomised to receive and not according to what they actually received, if different.
- The Per Protocol (PP) population will consist of all randomised patients who are evaluable for primary endpoint and who are considered not to have major protocol deviations (e.g. violation of major eligibility criteria, non-compliance to randomised treatment, use of forbidden drug…). The major protocol violations are patients who do not fulfill the diagnosis criteria for hand dermatitis, patients who have only mild disease at baselines or patients who use systemic immunosuppressants including oral corticosteroids during the study. The major protocol violations will be further defined in the SAP and validated by the coordinating investigator of the study.
- The Treated population will include all randomised patients who receive at least one dose of the study treatment (dupilumab or placebo). Subjects will be analysed according to the actual treatment received.

13.4. STATISTICAL METHODS

General approach

Study variables will be described by using the appropriate descriptive statistics according to the type of variable:

- Continuous variables: number of non-missing observations, mean, standard deviation, median, first and third quartile, minimum and maximum
- Categorical variables: number of non-missing observations, number and percentages of each modality (percentages will be calculated based on non-missing observations).

Descriptive tables will be displayed for the dupilumab group, for the placebo group and overall. More details on the variables to describe will be provided in the SAP.

Primary efficacy endpoint analysis

In primary efficacy analysis, the percentage change in mTLSS score from baseline to Week 16 will be compared between both groups using a covariance analysis including the group, the stratification factor (personal history of atopy) and the baseline mTLSS score as covariables. Treatment effect will be tested at a 5% significance level (confirmatory test). The ITT population will be used for this primary efficacy analysis. Missing data on mTLSS score at Week 16 will be replace using the Last-Observation-Carry-Forward (LOCF) imputation method.

Sensitivity analyses on primary efficacy endpoint

Three sensitivity analyses will be performed. In the first, multiple imputations method will be used to handle missing outcomes. In the second, no imputation of missing data will be done meaning that only patients evaluable for primary endpoint among the ITT population will be considered in the analysis. Finally, the efficacy analysis will be done on the Per-Protocol population.

Secondary efficacy endpoints analysis

Secondary efficacy endpoints will be tested without adjusting for multiplicity. There will be no fixed order of endpoints as this study is not considered a confirmatory phase III study.

The treatment effect on continuous secondary endpoints (i.e. change from baseline to Week 16 of pruritus, pain, quality of life, WPAI and EASI scores) will be estimated and tested using a covariance analysis including the group, the stratification factor and the baseline scores as covariables.

The treatment effect on binary secondary endpoints (i.e. clearance or almost clearance of CHE at Week-16 based on IGA or PaGa) will be estimated and tested using a Cochran Mantel-Haenszel test adjusted on the stratification factor used for randomization.

Secondary efficacy analyses will be performed on the Intention-To-Treat population. Methods to deal with missing data will be described in the SAP.

Safety analysis

The percentage of patients reporting the occurrence of treatment emergent adverse events classified by MedDRA System Organ Class (SOC) and Preferred Term (PT) will be presented by group with exact 95% Confidence Interval (CI) from study start to study end (Week-20 visit). No statistical test will be performed to compare incidences between groups due to the lack of power and issues with multiplicity testing.

The same table will be provided for adverse events of severe intensity and for adverse events related to study treatment.

The overall percentage of patients reporting at least one adverse event and at least one serious adverse event will also be computed with exact 95% CI.

All serious adverse events will be detailed in listings with start date, duration in days, intensity, causality assessment, action taken, outcome and dates of first and last study treatment administration.

The overall percentage of patients reporting injection site reactions will also be presented by group with exact 95% CI together with the evolution at 16 weeks since baseline of laboratory parameters (full blood count, transaminases, total IgE and specific IgE).

Safety analyses will be done on the treated population.

14. MONITORING THE STUDY

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. In accordance with International Conference on Harmonisation (ICH) guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and the sponsor is responsible for obtaining the agreement of all the parties involved in the study in order to guarantee direct access in all the sites where the study is being conducted to source data, source documents and reports, so that he can control their quality and audit them.

In this protocol, the absence of independent monitoring committee can be justified by:
- the study drug that is already marketed, with a known safety profile in a pathology (AD) close to that studied in the protocol
- close monitoring every 2 weeks
- injection during the visits with surveillance of a possible reaction to the injection or hypersensitivity.

The investigators will make available to the people with a right of access to these documents under the legislative and regulatory provisions in force (articles L.1121-3 and R.5121-13 of the French Public Health Act) the documents and individual data strictly necessary for monitoring, carrying out quality control and auditing the biomedical research.

14.1. SOURCE DATA

Any original document or object helping to prove the existence or accuracy of a piece of information or fact recorded during the study is defined as a source document.

The type of source document in the study will be medical record observations, original of scores, patient's diary or questionnaires fulfilled by the patient and/or the investigating doctor.

14.2. CONFIDENTIALITY OF DATA

In accordance with the legislative provisions in force (articles L.1121-3 and R.5121-13 of the French Public Health Code), people with direct access to source data will take all necessary precautions to ensure the confidentiality of information relating to investigational drugs, research studies and people taking part in them, particularly as regards their identity and the results obtained. These people, like the investigators themselves, are subject to professional secrecy.

During the biomedical research study or when it is over, the information collected on the people taking part in it and forwarded to the sponsor by the investigators (or any other specialist personnel involved) will be made anonymous. Under no circumstances may the uncoded names or addresses of the people concerned appear in it.

The sponsor will ensure that each person taking part in the study has given his agreement in writing for access to the individual data concerning him which is strictly necessary for quality control of the study.

15. QUALITY CONTROL AND ASSURANCE

15.1. INSTRUCTIONS FOR COLLECTING DATA

All the information required by the protocol must be entered in the case report forms and an explanation must be provided for each piece of information which is missing. The data must be collected as and when they are obtained, and transcribed into these forms in a clear and legible manner.
Incorrect data noted in the case report forms must be clearly crossed out and the new data copied in beside the crossed-out information, with the initials, date and possibly a reason, by the investigator or authorised person who has made the correction.

15.2. MONITORING THE STUDY

The study will be monitored by a clinical research technician. He will be responsible to the coordinating investigator for:

- the logistics of and monitoring the study,
- producing reports concerning its state of progress,
- verifying that the case report forms are updated (request for additional information, corrections, etc.),
- sending samples,
- transmitting SAEs to the sponsor.

He will work in accordance with the standard operating procedures, in cooperation with the clinical research associate appointed by the sponsor.

15.3. QUALITY CONTROL

A clinical research associate appointed by the sponsor will regularly visit each study centre during the process of setting up the study, one or more times during the study depending on the frequency of inclusions, and at the end of the study. During these visits, the following aspects will be reviewed:

- informed consent,
- compliance with the study protocol and the procedures set out in it,
- the quality of the data collected in the case report form: its accuracy, missing data, consistency of the data with the source documents (medical records, appointment diaries, the originals of laboratory results etc.),
- management of medicinal products if appropriate.

Each visit will be recorded in a written monitoring report.

15.4. DATA MANAGEMENT

Data will be collected into electronic Case Report Forms (eCRFs)

A validation plan which will detail precisely the checks for consistency which will be programmed by the Data Manager will be written and validated by the project coordinator and the statistician.
Data will be monitored. Queries will be generated and sent to the participating site. Responses to queries will be done in the database.

After data management, database will be locked and then be delivered to statistician for analysis in accordance with the statistical analysis plan.

15.5. AUDIT AND INSPECTION

An audit may be performed at any time by people appointed by the sponsor who are independent of those responsible for the study. The aim of an audit is to ensure the good quality of the study, that its results are valid and that the law and regulations in force are being observed.

The investigators agree to comply with the requirements of the sponsor and the relevant authority for an audit or an inspection of the study.

The audit can apply to all stages of the study, from development of the protocol to publication of the results and filing the data used or produced in the study.

16. ETHICAL AND REGULATORY CONSIDERATIONS

The sponsor and the investigator or investigators undertake to conduct this study in compliance with French law n° 2004-806 of 9th August 2004 and following Good Clinical Practice (I.C.H. version 4 of 1st May 1996 and the decision of 24th November 2006) and the Helsinki Declaration (Ethical Principles for Medical Research involving Human Subjects, Tokyo 2004).

The study is being conducted in accordance with this protocol. With the exclusion of emergency situations necessitating taking specific therapeutic actions, the investigator or investigators undertake to observe the protocol in all respects, in particular as regards obtaining consent and the notification and follow-up of serious adverse events.

This study was approved by the ethics committee of name of the ethics committee and was authorised by the ANSM.

Toulouse University Hospital, the sponsor of this study, has taken out an insurance policy covering third party liability with HDI Global SE complying with the provisions of article L1121-10 of the French Public Health Act.

The data recorded in this study are subject to computer processing by University Hospital of Toulouse in compliance with the Regulation 2016/679 of the European Parliament and of the council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) and the French Law "Informatique et Libertés" n°78-17 of 6th January 1978 amended .

This research falls within the framework of the "Reference methodology" (MR-001) in application of the provisions of article 54 paragraph 5 of the modified law of 6th January 1978 modified by law n°2018-493 of June 20th, 2018 concerning the computing, concerning the files and concerning the liberties modified as well as of the General regulation on the Data protection, the regulation N 2016/679 be adopted by the European Parliament on April 16th, 2016. This change has been approved by the decision of 5th January 2006. Toulouse University Hospital signed a commitment to comply with this "Reference methodology" on February 22th 2018.
This research is registered in the European EudraCT database under n° 2018-002830-19 in accordance with art. L1121.15 of the French Public Health Act.

- This research is registered on the web site http://clinicaltrials.gov/.

- The collection of physiological samples to be undertaken for this study was declared to ANSM at the same time as the request was made to authorise the study. After the study, conservation of the collection of physiological samples will be declared to the Minister for Research and to the director of the Regional Hospitalisation Agency (and submitted to the ethics committee for approval if there is any change in the aim of the study).

AMENDMENTS TO THE PROTOCOL

Any substantial modification, i.e. any modification of a nature likely to have a significant impact on the safety of the people involved, the conditions of validity and the results of the study, on the quality and safety of the investigational medicinal products, on interpretation of the scientific documents which provide support for the study or the methods for conducting it, is the subject of a written amendment to be submitted to the sponsor; prior to implementing it, the latter must obtain approval from the ethics committee and authorisation from ANSM.

Non-substantial modifications, i.e. those not having a significant impact on any aspect of the study whatsoever, are communicated to the ethics committee for information purposes.

Any amendments to the protocol must be made known to all the investigators participating in the study. The investigators undertake to comply with the contents.

Any amendment modifying the management of patients or the benefits, risks or constraints of the study is the subject of a new Patient Information and Informed Consent form which must be completed and collected according to the same procedure as used for the previous one.

17. STORAGE OF DOCUMENTS AND DATA CONCERNING THE STUDY

The following documents relating to this study are archived in accordance with Good Clinical Practice:

- By the investigating doctors:
  - **for a period of 15 years following the end of the study**
    - the protocol and any amendments to the protocol
    - the case record forms
    - the source files of participants who signed a consent form
    - all other documents and letters relating to the study
    - the original copies of informed consent forms signed by participants

  The investigator is responsible for all these documents for the regulation period of archiving.

- By the sponsor:
  - **for a period of 15 years following the end of the study**
    - the protocol and any amendments to the protocol
    - the originals of the case record files
    - All other documents and letters relating to the study
    - a copy of the informed consent forms signed by the participants
    - documents relating to serious adverse events

  The sponsor is responsible for all these documents for the regulation period of archiving.

No removal or destruction may be carried out without the sponsor's agreement. At the end of the regulation archiving period, the sponsor will be consulted regarding destruction. All the data, all the documents and reports could be subject to audit or inspection.

18. RULES RELATING TO PUBLICATION

18.1. SCIENTIFIC COMMUNICATIONS

Analysis of the data provided by the study centers is performed by the USMR (Unité de soutien Methodologique à la Recherche Clinique) of Toulouse hospital or a Contract Research Organisation with methodological contribution of the USMR and clinical contribution from the investigators. This analysis results in a written report which is submitted to the sponsor who transmits it to the ethics committee and the relevant authority.

Any written or oral communication of the results of the study must have been previously agreed by the coordinating investigator, the participating investigators, the methodologist and the biostatistician.

Publication of the main results should mention the name of the sponsor, all the investigators who recruited or monitored patients in the study, the methodologists, biostatisticians and data managers who took part in the study, the members of the committee or committees set up for the study and the participation of Sanofi/ Regeneron. The international rules for writing and publication (Vancouver Agreement, February 2006) will be taken into account. The determination of the qualifying rules to be an author will follow the ICMJE criteria.

18.2. COMMUNICATION OF THE RESULTS TO PATIENTS

In accordance with the law n° 2002-303 of 4th March 2002, patients are informed, at their request, of the overall results of the study.

18.3. CEDING DATA

The collection and management of data will be carried out by *Toulouse University Hospital*. The conditions for ceding all or part of the database of the study will be decided by the sponsor of the study and will be the subject of a written contract.

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APPENDICES

ANNEXE 1 : LIST OF INVESTIGATORS

Etude DUPECZEMAIN RC31/18/0269 - Version n° 5.0 du 19 avril 2022

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APPENDIX 2: PATIENT QUESTIONNAIRES

EVALUATION GLOBALE DU PATIENT

Cochez la case qui représente le mieux votre état actuel

Score	Intensité de l'eczema chronique des mains	Cocher la case appropriée
0	Aucune atteinte	
1	Très faible atteinte	
2	Légère atteinte	
3	Atteinte modérée	
4	Atteinte sévère	

QUESTIONNAIRE QUALITE DE VIE – DERMATOLOGIE

Ce questionnaire a pour but d'évaluer l'influence de votre problème de peau sur votre vie au cours des 7 derniers jours. Veuillez cocher une case par question.

1	Au cours des 7 derniers jours votre peau vous a-t-elle démangé(e), fait souffrir ou brulé(e)	Enormément Beaucoup Un peu Pas du tout	☐ ☐ ☐ ☐
2	Au cours des 7 derniers jours, vous êtes-vous senti(e) gêné(e) ou complexé(e)par votre problème de peau ?	Enormément Beaucoup Un peu Pas du tout	☐ ☐ ☐ ☐
3	Au cours des 7 derniers jours, votre problème de peau vous a-t-il gêné(e) pour faire des courses, vous occuper de votre maison ou pour jardiner	Enormément Beaucoup Un peu Pas du tout Non concerné	☐ ☐ ☐ ☐ ☐
4	Au cours des 7 derniers jours, votre problème de peau vous a-t-il influencé(e) dans le choix des vêtements que vous portiez ?	Enormément Beaucoup Un peu Pas du tout Non concerné	☐ ☐ ☐ ☐ ☐
5	Au cours des 7 derniers jours, votre problème de peau a-t-il affecté vos activités avec les autres ou vos loisirs ?	Enormément Beaucoup Un peu Pas du tout Non concerné	☐ ☐ ☐ ☐ ☐
6	Au cours des 7 derniers jours, avez-vous eu du mal à faire du sport à cause de votre problème de peau ?	Enormément Beaucoup Un peu Pas du tout Non concerné	☐ ☐ ☐ ☐ ☐
7	Au cours des 7 derniers jours, votre problème de peau vous a-t-il complètement empêché(e) de travailler ou d'étudier ?	Oui Non Non concerné	☐ ☐ ☐

	Si la réponse est « non » : au cours des 7 derniers jours, votre problème de peau vous a-t-il gêné(e) dans votre travail ou vos études	Beaucoup Un peu Pas du tout	☐ ☐ ☐
8	Au cours des 7 derniers jours, votre problème de peau a-t-il rendu difficiles vos relations avec votre conjoint(e), vos amis proches ou votre famille ?	Enormément Beaucoup Un peu Pas du tout Non concerné	☐ ☐ ☐ ☐ ☐
9	Au cours des 7 derniers jours, votre problème de peau a-t-il rendu votre vie sexuelle difficile ?	Enormément Beaucoup Un peu Pas du tout Non concerné	☐ ☐ ☐ ☐ ☐
10	Au cours des 7 derniers jours, le traitement que vous utilisez pour votre peau a-t-il été un problème, par exemple en prenant trop de votre temps ou en salissant votre maison ?	Enormément Beaucoup Un peu Pas du tout Non concerné	☐ ☐ ☐ ☐ ☐

ECHELLE VISUELLE ANALOGIQUE DE LA DOULEUR CUTANEE (EVA)

Veuillez préciser l'intensité globale de votre douleur cutanée due à votre eczema chronique des mains au moment present en plaçant une marque sur l'échelle horizontale (0= aucune douleur cutanée; 100 = douleur cutanée intense)

ECHELLE VISUELLE ANALOGIQUE DE LA PERTE DE SOMMEIL (EVA)

Veuillez préciser l'intensité globale de votre perte de sommeil due à votre eczema chronique des mains au moment present en plaçant une marque sur l'échelle horizontale (0= aucun trouble du sommeil; 100 = perte de sommeil intense)

ECHELLE VISUELLE ANALOGIQUE DU PRURIT (EVA)

Veuillez préciser l'intensité globale de votre prurit (démangeaison) due à votre eczema chronique des mains au moment present en plaçant une marque sur l'échelle horizontale (0= aucune démangeaison; 100 = démangeaison intense)

0	100
Aucune démangeaison	Démangeaison intense

WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: GENERAL HEALTH V2.0 (WPAI:GH)
Questionnaire sur la baisse de productivité au travail et la limitation des activités: Santé générale V2.0 (WPAI :GH°)

Les questions suivantes portent sur les conséquences de vos problèmes de santé sur votre capacité à travailler et à effectuer vos activités habituelles. Par problème de santé, nous entendons tout problème ou symptôme physique ou émotionnel. *Veuillez, selon les questions, encercler le nombre qui convient ou compléter les espaces appropriés comme indiqué.*

1) Occupez-vous un emploi (travail rémunéré) en ce moment? ____ NON ___ OUI
Si vous répondez NON, cochez « NON » et passez directement à la question 6.

Les questions qui suivent portent sur les **sept derniers jours**, sans compter aujourd'hui.

2) Au cours des sept derniers jours, combien d'heures de travail, au total, avez-vous manquées à cause de vos problèmes de santé? *Comptez les heures d'absence pour congé de maladie, les retards et départs précoces du travail, etc. dus à vos problèmes de santé. Ne comptez pas les moments où vous vous êtes absenté(e) pour participer à cette étude.*

_____ HEURES

3) Au cours des sept derniers jours, combien d'heures de travail avez-vous manquées pour toute autre raison que vos problèmes de santé telle qu'un congé, des vacances ou la participation à cette étude?

_____ HEURES

4) Au cours des sept derniers jours, combien d'heures de travail au total avez-vous effectuées?

_____ HEURES (*Si votre réponse est « 0 », passez directement à la question 6.)*

5) Au cours des sept derniers jours, dans quelle mesure vos problèmes de santé ont-ils affecté votre productivité pendant que vous étiez en train de travailler? *Tenez compte des jours pendant lesquels vous avez été limité(e) dans la quantité ou le type de travail que vous auriez pu accomplir, vous en avez fait moins que vous l'auriez souhaité ou vous ne pouviez pas travailler aussi soigneusement que d'habitude. Si vos problèmes de santé n'ont eu qu'une faible incidence sur votre travail, choisissez une note peu élevée. Choisissez une note élevée si vos problèmes de santé ont beaucoup perturbé votre travail.*

Tenez uniquement compte de la manière dont vos problèmes de santé ont diminué votre productivité pendant que vous étiez en train de travailler.

Mes problèmes de santé n'ont eu aucun effet sur mon travail	0	1	2	3	4	5	6	7	8	9	10	À cause de mes problèmes de santé, je n'ai pas pu travailler du tout

ENCERCLEZ UN NOMBRE

6) Au cours des sept derniers jours, dans quelle mesure vos problèmes de santé ont-ils affecté votre capacité à effectuer vos activités quotidiennes habituelles en dehors de votre lieu de travail? *Par activités habituelles, nous entendons les activités que vous effectuez régulièrement, telles que les travaux ménagers, les courses, l'exercice, s'occuper des enfants, étudier, etc. Tenez compte des moments où vous avez été limité(e) dans la quantité ou le type d'activités que vous auriez pu accomplir et de ceux où vous en avez fait moins que vous l'auriez souhaité. Si vos problèmes de santé n'ont eu qu'une faible incidence sur vos activités, choisissez une note peu élevée. Choisissez une note élevée si vos problèmes de santé ont beaucoup perturbé vos activités.*

Tenez uniquement compte de la manière dont vos problèmes de santé ont diminué votre capacité à effectuer vos activités quotidiennes habituelles en dehors de votre lieu de travail.

Mes problèmes de santé n'ont eu aucun effet sur mes activités quotidiennes	0	1	2	3	4	5	6	7	8	9	10	À cause de mes problèmes de santé, je n'ai pas du tout pu me consacrer à mes activités quotidiennes

ENCERCLEZ UN NOMBRE

QUESTIONNAIRE SUR L'ETAT DE SANTE (EQ-5D-5L)

Veuillez indiquer, pour chacune des rubriques suivantes, l'affirmation qui décrit le mieux votre état de santé aujourd'hui, en cochant la case appropriée.

Mobilité (choix unique)

□ Je n'ai aucun problème pour me déplacer à pied
□ J'ai de légers problèmes pour me déplacer à pied □
□ J'ai des problèmes modérés pour me déplacer□
□ J'ai des problèmes sévères pour me déplacer□
□ Je suis obligé (e) de rester allité(e)

Autonomie

□ Je n'ai aucun problème pour prendre soin de moi
□ J'ai de légers problèmes pour me laver ou m'habiller seul(e)
□J'ai des problèmes modérés pour me laver ou m'habiller seul(e)
□ J'ai des problèmes sévères pour me laver ou me déplacer seul(e)
□ Je suis incapable de me laver ou m'habiller seul(e)

Activités courantes (exemple : travail, études, travaux domestiques, activités familiales ou loisirs)

□ Je n'ai aucun problème pour accomplir mes activités courantes
□ J'ai de légers problèmes pour accomplir mes activités courantes
□ J'ai des problèmes modérés pour accomplir mes activités courantes
□ J'ai des problèmes sévères pour accomplir mes activités courantes
□ Je suis incapable d'accomplir mes activités courantes

Douleurs / gêne

□ Je n'ai ni douleur ni gêne
□ J'ai des douleurs ou gêne légère(s)
□ J'ai des douleurs ou gêne modérée(s)
□ J'ai des douleurs ou gêne sévère (s)
□ J'ai des douleurs ou gêne extrême(s)

Anxiété /Depression

□ Je ne suis ni anxieux(se) ni déprimé(e)
□Je suis légèrement anxieux(se) ou déprimé(e)
□ Je suis modérément anxieux(se) ou déprimé(e)
□ Je suis sévèrement anxieux(se) ou déprimé(e)
□ Je suis extrêmement anxieux(se) ou déprimé(e)

Pour vous aider à indiquer dans quelle mesure tel ou tel état de santé est bon ou mauvais, nous avons tracé une échelle graduée (comme celle d'un thermomètre) sur laquelle 100 correspond au meilleur état de santé que vous puissiez imaginer et 0 au pire état de santé que vous puissiez imaginer.

Nous aimerions que vous indiquiez sur cette échelle où vous situez votre état de santé aujourd'hui. Pour cela, veuillez tracer une ligne allant de l'encadré ci-dessous à l'endroit qui, sur l'échelle, correspond à votre état de santé aujourd'hui.

Votre état de santé aujourd'hui