A phase 3 extension trial of DELTA 1 and DELTA 2 to evaluate the long-term safety of a twice-daily treatment with delgocitinib cream 20 mg/g as needed for up to 36 weeks in adult subjects with chronic hand eczema (DELTA 3)

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Primary objective:To evaluate the long-term safety of an as-needed treatment with twice-daily applications of delgocitinib cream 20 mg/g.Secondary objective:To evaluate the long-term efficacy of an as-needed treatment with twice-daily applications...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Epidermal and dermal conditions
Study type	Interventional

Summary

ID

NL-OMON51146

Source
ToetsingOnline

Brief title
DELTA3

Condition

- Epidermal and dermal conditions

Synonym
Chronic handeczema

Research involving

Human

Sponsors and support

Primary sponsor: Leo Pharma
Source(s) of monetary or material Support: LEO Pharma

Intervention

Keyword: Adults, Chronic handeczema, Delgocitinib, Extension

Outcome measures

Primary outcome

Number of treatment-emergent AEs from baseline up to Week 38.

Secondary outcome

• IGA-CHE score at each scheduled visit from baseline up to Week 36.

• IGA-CHE score of 0 (clear) or 1 (almost clear) at each scheduled visit from

baseline up to Week 36.

• HECSI score at each scheduled visit from baseline up to Week 36.

• HECSI-75 at each scheduled visit from baseline up to Week 36

• HECSI-90 at each scheduled visit from baseline up to Week 36.

Study description

Background summary

Chronic hand eczema (CHE) is a serious inflammatory skin disorder located anywhere on the hands or wrists. In the acute stage, it is clinically characterised by erythema, infiltration,oedema, or vesicles, and in the chronic stage by scaling, fissures, and hyperkeratosis, and the condition may be exacerbated by bacterial infections. Important symptoms include itch and pain, and the disease is often characterised by relapses and a poor prognosis. CHE refers to hand eczema which persists for more than 3 months or returns twice or more often within 12 months (1).
Hand eczema aetiology is usually multifactorial, and it is generally agreed

that no simple relationships exist between clinical patterns and aetiological diagnoses (2). Several different classifications have been proposed (1, 3, 4), however it is generally agreed that the most
common subtypes of CHE are contact dermatitis (irritant and allergic), atopic hand eczema, and hyperkeratotic eczema (5). Other subtypes include acute recurrent vesicular hand eczema, and contact urticaria/protein contact dermatitis (1).
The reported prevalence and incidence rates of hand eczema vary considerably, depending on the methodology in the collection of data. In a review of data available from 1964 to 2007, the prevalence of hand eczema in the general population was approximately 4%, 1-year prevalence about 10%, and life-time prevalence approached 15% (6). In another study by Thyssen et al. (7), approximately 7-10% of patients with hand eczema reported symptoms *nearly all the time*, implying a chronic state of the disease. Based on data from 7 studies, the incidence rate of hand eczema was 5.5 cases/1000 person-years with a higher median incidence rate among women (1). Several risk factors, such as pre-existing atopic dermatitis (AD), female sex, wet work, and contact allergy have been identified (6, 8). The prevalence of hand eczema is different across age groups (6) with a mean/median first onset in the early or mid-20*ies (9-11). However, approximately one-third of men and women report their first hand eczema before the age of 20 (12). The socioeconomic burden of CHE is significant. 5 studies from 4 countries have found that total societal costs (direct and indirect) ranged between USD $1,924 and USD $8,212 (inflated to 2017 cost) per patient per year (1, 13-16). CHE is associated with increased sick leave (17, 18) as well as job loss and change in jobs (5, 19, 20).
Overall, CHE has a significant detrimental effect on health-related quality of life (HRQoL), work productivity, daily activities, and health care costs (13).
Although the molecular mechanisms underlying CHE are not fully understood, a large panel of cytokine-mediated signalling cascades have been identified as part of the pathophysiology, including cytokine responses representing Th2 pathway (IL-4, IL-13), Th22 pathway (IL-22), Th17 pathway (IL-17), Th1 pathway (interferon-γ), and the JAK/STAT (janus kinase/signal transducer and activator of transcription) pathway. As the JAK proteins are required for signalling of most cytokines, blocking of JAKs reduces cytokine signalling and thereby abrogates the vicious cycle that leads to the development of CHE (21-23).
CHE is generally difficult to treat and presents with periods of flares and periods of remissions. Long-term disease control of CHE may require reactive treatment of flares and proactive treatment for the prevention of flares.
Treatment of CHE involves different disease management strategies such as elimination of triggers, general skin care, and anti-inflammatory therapy in a step-wise approach. General skin care in terms of emollients is widely used and recommended by physicians, but evidence of efficacy is sparse (1). Elimination of triggers such as allergens and irritants is a necessary prerequisite for successful therapy on a longer term. Topical corticosteroids (TCS) remain the mainstay of topical anti-inflammatory therapy for hand eczema. However, long-term use of TCS is restricted due to side effects such as skin atrophy and potential inhibition of skin barrier repair (24). Whereas mild CHE to some

extent may be managed by elimination of triggers, general skin care, and TCS, management of moderate to severe CHE is more cumbersome. Alitretinoin (25) is the only approved product specifically indicated for treatment of CHE but is only indicated for severe CHE unresponsive to treatment with potent TCS, and only approved in Europe and a few other countries worldwide.
Considering the paucity of approved therapies for the treatment of CHE, other therapeutic options are limited to those approved for other skin diseases with an inflammatory pathophysiology. These applied treatments lack the clinical documentation for use in CHE.
As the currently available treatment options either lack documented treatment effect or are limited by restrictions of long-term use due to safety concerns (1, 26), there is a high unmet medical need for new topical treatment of moderate to severe CHE with high efficacy in combination with a good safety profile especially for long-term use. New and better treatments would potentially improve HRQoL of patients with moderate to severe CHE.Delgocitinib has the potential to address the unmet medical need associated with this burdensome disease.

Study objective

Primary objective:
To evaluate the long-term safety of an as-needed treatment with twice-daily applications of delgocitinib cream 20 mg/g.

Secondary objective:
To evaluate the long-term efficacy of an as-needed treatment with twice-daily applications of delgocitinib cream 20 mg/g.

Other/exploratory objectives:
To explore efficacy, health-related quality of life, and work productivity for an as needed treatment with twice-daily applications of delgocitinib cream 20 mg/g.

Study design

This trial is a phase 3, open-label, multi-site, extension trial. The trial is designed to evaluate the long-term safety of twice-daily applications of delgocitinib cream 20 mg/g as needed in eligible subjects with CHE who completed one of the 2 pivotal phase 3 trials with delgocitinib cream 20 mg/g or cream vehicle (parent trials - LP0133-1401 or LP0133-1402). The trial will include a screening period of up to 4 weeks (Week -4 to Week 0) and a treatment period of 36 weeks during which subjects will be treated with delgocitinib cream 20 mg/g twice daily as needed. During the treatment period, subjects will attend site visits every 4 weeks; if needed, unscheduled visits will be performed to initiate or stop treatment with delgocitinib cream 20 mg/g twice daily. Subjects will attend an end-of-treatment visit at Week 36 and a safety

follow-up will be performed by phone approximately 2 weeks after the end-of treatment visit to assess any AEs.

Screening period (Week -4 to Week 0)

Eligibility will be assessed at screening and at the baseline visit. To facilitate a smooth transition between completing treatment in the parent trial and commencing participation in the extension trial, potentially eligible subjects will be offered participation in the extension trial preferably at the Week 12 visit (prior to the end-of-treatment visit at Week 16) in the parent trial. Hence, the screening period is expected to overlap with the last 4 weeks of the treatment period in the parent trial. Any assessment from the Week 12 visit performed in the parent trials may be used to confirm eligibility for this extension trial. However, if for any reason, assessments from the Week 12 visit are not evaluable, the Week 16 assessments from the parent trials may be used as screening results for this trial, without precluding the initial enrolment of the subject in this extension trial. The end-of-treatment visit in the parent trial will coincide with the baseline visit of the extension trial. For subjects meeting the eligibility criteria (those which can be evaluated prior to the end-of-treatment visit [Week 16] in the parent trials), assessments performed at the end-of-treatment visit in the parent trial may be re-used without being repeated for this extension trial. The subjects will have their eDiary from the parent trial updated to record PROs, treatment compliance, and local tolerability in this extension trial. Completion of the eDiary will be initiated from the baseline visit (Day 1).

Treatment period (Week 0 up to Week 36)

Definition of terms:
Response is defined as IGA-CHE score of 0 (clear) or 1 (almost clear).
Treatment re-initiation is triggered by an IGA-CHE score of >=2 after having achieved
IGA-CHE 0 (clear) or 1 (almost clear) in this trial.

At baseline (Day 1), subjects will be evaluated by the investigator to determine the severity of their CHE. Subjects with IGA-CHE score of 0 (clear) or 1 (almost clear) will not be assigned treatment with delgocitinib cream 20 mg/g; they will however continue to use their routine skin care emollient, if applicable. Subjects with IGA-CHE score >=2 will start treatment with twice-daily delgocitinib cream 20 mg/g. Treatment will continue until IGA-CHE score of 0 (clear) or 1 (almost clear) is achieved.

If a subject experiences worsening of CHE signs and symptoms while off-treatment, the subject should contact the trial site. If a scheduled visit is not planned within a reasonable timeframe, an unscheduled visit should be planned as soon as possible. If an IGA-CHE score >=2 is attested, the subject will be dispensed delgocitinib cream 20 mg/g and the investigator will instruct

the subject to start treatment with twice-daily applications. The minimal set of assessments to be performed at an unscheduled visit to decide if treatment with delgocitinib cream 20 mg/g should be re-initiated is IGA-CHE and collection of AEs.

While on treatment with delgocitinib cream 20 mg/g, if the subject observes that CHE signs and symptoms are resolved, they should contact the trial site. If a scheduled visit is not planned within a reasonable timeframe, an unscheduled visit should be planned as soon as possible. If IGA-CHE score of 0 (clear) or 1 (almost clear) is achieved, the subject will be instructed to stop treatment and return all opened and unopened tubes to the site. The minimal set of assessments to be performed at an unscheduled visit to decide if treatment with delgocitinib cream 20 mg/g should be stopped is IGA-CHE, collection of AEs, and investigator*s assessment of local tolerability.

For all subjects, regardless if on- or off-treatment, IGA-CHE will be evaluated by the investigator at visits to the trial site every 4 weeks from baseline up to Week 36.

If no improvement is observed after a continuous treatment period of 16 weeks with twice-daily delgocitinib cream 20 mg/g, it will be at the discretion of the investigator to evaluate if the subject will benefit from further treatment with delgocitinib cream 20 mg/g.

If CHE becomes *intolerable*, the subject should contact the investigator for an unscheduled visit. Rescue treatment for CHE may be provided to subjects at the discretion of the investigator. In this case, delgocitinib cream 20 mg/g will be discontinued immediately and the subject will be withdrawn from the trial.

At Week 36, subjects will attend an end-of-treatment visit. If treatment for CHE is required beyond the end-of-treatment visit, subjects will be referred to standard of care treatment at the discretion of the investigator.

Follow-up period (Week 36 to Week 38)

All subjects will complete a 2-week off-treatment follow-up period for the assessment of safety. The safety follow-up period will start after the Week 36 visit (end-of-treatment). Note that for subjects who permanently discontinue delgocitinib cream 20 mg/g, the 2-week follow-up period will start at the time of the early termination visit. The safety follow-up visit will be performed via phone, but can be a site visit if needed.

Intervention

Name of IMP: delgocitinib cream
Active substance: delgocitinib

Dosage form: cream
Concentration: 20 mg / g
Dose and method of administration: apply topically twice daily

Study burden and risks

There is a clear unmet medical need for new long-term therapies for subjects with moderate to severe CHE. The only currently approved treatment option indicated for patients with CHE is alitretinoin, which is associated with significant safety precautions and is only indicated for severe CHE. Alitretinoin is only approved in Europe and a few countries worldwide. Delgocitinib is a topically applied JAK inhibitor. Systemic JAK inhibitors are associated with potential adverse reactions and a black box warning concerning the risk of serious infections, malignancy, and thrombosis. These risks are not considered relevant for delgocitinib cream due to the very low systemic exposure observed in previous trials with topically applied delgocitinib. No important identified risks of delgocitinib have been documented during the overall nonclinical and clinical development to date. A detailed overview of nonclinical and clinical data on delgocitinib is available in the current investigator*s brochure (33). The risk to subjects in this trial will be minimised by fulfilment of all eligibility criteria and by close clinical monitoring. To ensure the safety and wellbeing of subjects participating in this trial, safety will be monitored during the trial, and stopping criteria have been defined (Section 10.2).
The blood sampling procedure poses the same low risk as normally associated with this procedure (i.e. infection, bleeding into the surrounding tissue, and, very rarely, inflammation of the vein or formation of blood clots). Blood sampling will be conducted by qualified medical personnel.
Altogether, the risks associated with participating in this clinical trial are considered low and are expected to be outweighed by the benefit of a potential future treatment option for CHE.Participation in clinical trials may currently be associated with increased risk and added challenges due to the COVID-19 pandemic caused by SARS-CoV-2. The proposed trial and treatment with delgocitinib cream 20 mg/g are not believed to put subjects with CHE at an increased risk for viral infections including SARS-CoV-2. However, a risk of exposure to infected people cannot be excluded as the trial subjects may enter public areas (e.g. commute to the trial site) and have additional human contact (e.g. with trial site staff). Appropriate risk assessments and mitigation measures must be considered to protect the subjects and trial site staff and to ensure the integrity of the trial data. Both EMA (34) and FDA (35) as well as national health authorities in Europe have issued new guidelines that aim to provide recommendations for conduct of clinical trials during the COVID-19 pandemic. Given the circumstances of the potentially relapsing pandemic situation with regard to the spread of COVID-19 in the future, special attention will be paid to protecting subjects participating in the trial and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the newly issued EMA guideline. During the trial, the

investigators will be trusted to take appropriate actions to ensure the safety of the individual subjects according to local authority-issued preventive measures. As these can differ across countries and regions, no general instruction from the sponsor can be provided concerning subject safety and the need for postponing trial visits. In case of local authority-issued preventive measures, the investigator can convert on-site visits into phone or video consultations. At phone/video visits, no investigator assessments of efficacy can be done. Therefore, if and only if subjects are prevented from attending on-site visits due to local authority-issued preventive measures, a decision to start or stop treatment with delgocitinib 20 mg/g can be taken based on a phone or video visit. Safety monitoring remains an obligation to LEO Pharma, and it is considered feasible to collect safety data remotely (via electronic communication) where on-site visits are not possible. Other mitigating measures include collecting patient-reported outcome (PRO) data via a web-based solution and ensuring supply of IMP to the subjects to overcome local authority-issued preventive
measures due to the COVID-19 pandemic (see Appendix 7 for details).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Signed and dated informed consent has been obtained prior to any protocol-related procedures.
2. The baseline visit in this extension trial must coincide with the Week 16 (end-of-treatment) visit in the parent trial.
3. Subjects must have met eligibility criteria at screening and baseline in the parent trial.
4. Subjects must have completed the treatment period in the parent trial (to be assessed at
baseline visit in this extension trial).
5. Subjects must have complied with the clinical trial protocol in the parent trial to the
satisfaction of the investigator.
6. A woman of childbearing potential* must use an acceptable** method of birth control
throughout the trial up until the end-of-treatment/early termination visit.

Exclusion criteria

1. Subjects who prematurely discontinued treatment with IMP or initiated rescue medication in the parent trial.
2. Subjects who experienced any adverse event (AE) during participation in the parent trial, which precludes further treatment with delgocitinib cream 20 mg/g in the judgement of the investigator.
3. Any medical or psychiatric condition that could put the subject at undue risk by participating in the trial, or which, by the investigator's judgment, makes the subject inappropriate for the trial.
4. Current participation in any other interventional clinical trial, except for parent trial.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-01-2022
Enrollment:	29
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Delgocitinib
Generic name:	N/A

Ethics review

Approved WMO Date:	31-05-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-08-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2021

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-002962-15-NL
CCMO	NL76050.018.21