New Clinical End-points in patients with primary Sjögren*s Syndrome: an Interventional Trial based on stratifYing patients

Published: 23-07-2021
Last updated: 25-09-2024

This study has been transitioned to CTIS with ID 2023-510054-16-00 check the CTIS register for the current data. Primary objective:To evaluate the efficacy of each active treatment combination (hydroxychloroquine + leflunomide and hydroxychloroquine...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON55055

Source
ToetsingOnline

Brief title
Necessity

Condition

- Autoimmune disorders

Synonym
Sjogren's syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Assistance Publique_Hôpitaux de Paris (APHP), by delegation Clinical

Research and Innovation Direction (DRCI)
Source(s) of monetary or material Support: Innovative Medicines Initiative 2 consortium (IMI2)

Intervention

Keyword: auto-immune, primary Sjögren's Syndrome

Outcome measures

Primary outcome

Primary endpoints:

Each cohort is analysed separately

* Cohort 1: Proportion of patients achieving a response according to

preliminary STAR at week 24 between each active treatment arm and placebo arm.

* Cohort 2: Proportion of patients achieving a response according to

preliminary STAR at week 24 between each active treatment arm and placebo arm.

Secondary outcome

Secondary endpoints:

Cohorts 1 and 2 together

* Cohort 1 and 2: Proportion of patients achieving a response according to

preliminary STAR at week 24 between each active treatment arm and placebo arm.

Cohorts 1 and 2 (the two cohorts will be analysed separately):

* Proportion of patients achieving a response according to preliminary STAR

from baseline at week 12 and 36 between each active treatment arm and placebo

arm.

* Change in ESSPRI from baseline at week 12, 24 and 36 between each active

treatment arm and placebo arm. The difference of ESSPRI score at week 12, 24

and 36 (adjusted for baseline value) will be also compared between each active

treatment arm and placebo arm.

* Proportion of patients achieving a response in ESSPRI (defined as a decrease of ESSPRI score of >= 1 (or >= 15%)) from baseline at week 12, 24 and 36 between each active treatment arm and placebo arm.

* Change in ESSDAI/clinESSDAI from baseline at week 12, 24 and 36 between each active treatment arm and placebo arm. The difference of ESSDAI/clinESSDAI score at week 12, 24 and 36 (adjusted for baseline value) will be also compared between each active treatment arm and placebo arm.

Cohort 1: This analysis will be performed only if the number of patients with ESSDAI/clinESSDAI > 0 is sufficient.

* Proportion of patients achieving a response in ESSDAI/clinESSDAI (defined as improvement of ESSDAI/clinESSDAI >= 3 points) from baseline at week 12, 24 and 36 between each active treatment arm and placebo arm.

* Discriminant capacity of STAR (preliminary STAR and alternate options) relative to ESSDAI (clinESSDAI)/ESSPRI at week 24 and 36 to detect changes in the placebo arm versus in each active treatment arm in each cohort and globally

Change in unstimulated whole salivary flow from baseline at week 12, 24 and 36 between each active treatment arm and placebo arm.

* Change in Schirmer*s score from baseline at week 12, 24 and 36 between each active treatment arm and placebo arm.

* Change in Tear Break-up time score from baseline at week 24 and 36 between each active treatment arm and placebo arm.

* Change in Ocular Staining Score from baseline at week 24 and 36 between each active treatment arm and placebo arm.

* Change in score of HADS questionnaire from baseline at week 12, 24 and 36 between each active treatment arm and placebo arm.

* Change in score of EQ-5D-5L questionnaire from baseline at week 12, 24 and 36 between each active treatment arm and placebo arm.

* Change in symptoms collected using the PEPSS WebApp from baseline to week 24 between each active treatment arm and placebo arm.

Exploratory endpoints:

Cohorts 1 and 2 (the two cohorts will be analysed separately):

* Proportion of patients achieving a response in STAR alternate options 1, 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 14, 15, 16 and 17 from baseline at week 12, 24 and 36 between each active treatment arm and placebo arm.

* Change in STAR alternate options 6, 11, 18 and 19 from baseline at week 12, 24 and 36 between each active treatment arm and placebo arm. The difference of STAR score at week 12, 24 and 36 (adjusted for baseline value) will be also compared between each active treatment arm and placebo arm.

* Validation of the final STAR

* Change in oral dryness and ocular dryness Visual Analog Scale (VAS) from baseline at week 12, 24 and 36 between each active treatment arm and placebo arm.

* Change in PhGA from baseline at week 12, 24 and 36 between each active treatment arm and placebo arm.

* Change in PatGA from baseline at week 12, 24 and 36 between each active treatment arm and placebo arm.

* Change in SSSD from baseline at week 24 and 36 between each active treatment arm and placebo arm.

* Proportion of patients considered as improved according to patient opinion and physician evaluation of change at week 24 and week 36

* Change in meibography measurements from baseline at week 24 between each active treatment arm and placebo arm.

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Version date: April 2018

* Change in non-invasive tear break-up time measurements from baseline at week 24 between each active treatment arm and placebo arm.

* Change in the novel ultrasound scoring system (SGUS) from baseline at week 24 between each active treatment arm and placebo arm.

* Change in the measurements collected with the two biosensors as surrogate measures of fatigue from baseline at week 12 and 24 between each active treatment arm and placebo arm.

* Change in levels of several biomarkers from baseline at week 24 between each active treatment arm and placebo arm.

* Change in the salivary gland histologic abnormalities from baseline at week 24 between each active treatment arm and placebo arm.

* Change in score of OSDI questionnaire from baseline at week 24 and 36 between each active treatment arm and placebo arm.

* Change in score of FSFI questionnaire from baseline at week 24 and 36 between

each active treatment arm and placebo arm.

Study description

Background summary

There are no approved treatments for pSS and the clinical endpoints currently used in clinical trials are inadequate to capture all aspects of the disease that should be evaluated in clinical trials. The newly developed composite endpoint: Sjögren*s Tool for Assessing Response to treatment (STAR) will allow a more specific and meaningful assessment of treatment efficacy in pSS. Because of the heterogeneity of the disease and of the central role of the interplay between B- and T-cells in the pathogenesis, it is worth to evaluate combination of conventional synthetic immunomodulatory drugs targeting both B- and T-cells.

Study objective

This study has been transitioned to CTIS with ID 2023-510054-16-00 check the CTIS register for the current data.

Primary objective:
To evaluate the efficacy of each active treatment combination (hydroxychloroquine + leflunomide and hydroxychloroquine + mycophenolate mofetil) based on proportion of responder patients according to preliminary STAR at week 24.

Secondary objectives:
Cohort 1 and 2 together:
To evaluate the efficacy of each active treatment combination based on proportion of responder patients according to preliminary STAR at week 24.
Cohorts 1 and 2 separately:
* To evaluate the efficacy of each active treatment combination at week 12 and 36 based on proportion of responder patients according to preliminary STAR.
To evaluate the efficacy of each active treatment combinations at week 12, 24 and 36 based on change in ESSPRI.
* To evaluate the efficacy of each active treatment combination at week 12, 24 and 36 based on change in ESSDAI/clinESSDAI.
* To assess the discriminant capacity of STAR (preliminary STAR and alternate options) relative to ESSDAI (clinESSDAI)/ESSPRI to detect changes at week 24 and 36.
* To evaluate the effect of each active treatment combination on glandular function at week 12, 24, 36.
* To evaluate the effect of each active treatment combination on anxiety and

depression, health-related quality of life at week 12, 24 and 36.
* To evaluate the utility of the PEPSS WebApp in collecting symptoms on a daily basis over 24 weeks.

Study design

Randomized double-blind controlled trial. Patients are stratified in 2 cohorts and randomized between 3 arms:
* triple placebo,
* hydroxychloroquine (HCQ) 400mg/d, leflunomide (LEF) 20mg/d and placebo of mycophenolate mofetil (MMF),
* or hydroxychloroquine 400mg/d, mycophenolate mofetil 2000mg/d and placebo of leflunomide.
The duration of the treatment will be 24 weeks. Patients will be followed up until week 36 (12 weeks after the end of treatment period).

Intervention

Investigational medicinal product(s)
- Hydroxychloroquine: Plaquenil* 200 mg tablets
* Mycophenolate Mofetil 500 mg tablets
* Leflunomide 20 mg tablets

Comparator treatment
- Oral placebo tablets for HCQ, LEF and MMF

Interventions added for the trial
* ESSDAI/ClinESSDAI, PhGA, STAR scores, Physician evaluation of change
* Patient questionnaires (ESSPRI, VAS (ocular and oral dryness), PatGA, HADS, FSFI, EQ-5D-5L, OSDI, SSSD, Patient*s opinion)
* Schirmer*s test, unstimulated whole salivary flow, Tear Break Up Time (TBUT), Ocular Staining Score (OSS)
* Non-invasive TBUT, meibography (optional)
* PEPSS webapp (optional)
* Biosensors (UK centres only, optional)
* Ultrasound salivary gland (optional)
* Minor salivary gland biopsy (optional)
* Blood collection (serum, RNA)

Study burden and risks

The risk level of the research was estimated as high
Hydroxychloroquine, leflunomide and mycophenolate mofetil are frequently given off label to patients with pSS. Their safety profile is well known so the risks for the patient will be minimal.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Cohort 1
- Having given written informed consent prior to undertaking any study-related procedures.
- Patients with pSS according to ACR/EULAR 2016 criteria or AECG 2002 criteria (see addenda 4)
- With a high level of symptoms (ESSPRI >= 5) and low systemic disease activity (ESSDAI < 5).
- Negative pregnancy test (serum at screening)
- Use highly reliable contraception (as defined in section 6.3) during research treatment from the screening and for two years after stopping treatment.

Cohort 2
- Having given written informed consent prior to undertaking any study-related procedures.
- Patients with pSS according to ACR/EULAR 2016 criteria or AECG 2002 criteria (see addenda 4)
- With moderate/high systemic disease activity, as defined by ESSDAI >= 5.
- Negative pregnancy test (serum at screening)
- Use highly reliable contraception (as defined in section 6.3) during research treatment from the screening and for two years after stopping treatment.

Exclusion criteria

For both cohorts:
- Age < 18 years
- Pregnant or breastfeeding women or women wanted to conceive either during or within two years after the end of the treatment period
- Women of childbearing potential not using highly effective methods of contraception (as defined in section 6.3)
- Participation in another interventional trial
- Contra-indication to HCQ: pre-existing retinopathy, hypersensitivity to HCQ or to any of the excipients of the specialty used
- Contra-indication to MMF: hypersensitivity to mycophenolate mofetil, acid mycophenolic, mycophenolate sodium or to any of the excipients of the specialty used
- Contra-indication tor LEF: hypersensitivity to the active substance, the main active metabolite teriflunomide or to any excipients of the specialty used.
- Concomitant treatment with corticosteroids more than 10 mg/day of prednisone equivalent at screening or inclusion (randomisation)
- Concomitant treatment with other immunomodulators including methotrexate, azathioprine, cyclophosphamide, cyclosporine and tacrolimus
- Previous treatment with HCQ, LEF, MMF in the last 3 months
- Previous treatment with rituximab, other B-cell targeted biologic therapy or cyclophosphamide in the last 6 months
- Previous treatment with anti-TNF, abatacept, tocilizumab or belimumab or any other biologic in the setting of a past clinical trial in the last 3 months
- Severe life-threatening systemic involvement requiring cyclophosphamide or high dose corticosteroids, or any drug considered as an exclusion criteria
- Impairment of other severe immunodeficiency states
- Patients with active malignancy or history of malignancy within the last 5 years except non-melanoma skin cancer
- Patients with history of gastrointestinal tract ulceration, hemorrhage and perforation
- Patients with history of cardiomyopathy
- Patients with known hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller

syndrome
- Serious infection in the past month
- Evidence of active tuberculosis infection
- Active HCV (positive PCR)
- Active HBV infection (positivity for HBS antigen, or positivity for anti-HBC antibody without any HBS antigen)
- HIV infection (positive serology)
- Positive SARS-Cov2 PCR (if vaccinated for COVID-19, no PCR is required; if history of COVID-19 infection, positive serology is sufficient)
- Cytopenia defined as neutrophils < 1.0 G/L, lymphocytes < 0.5 G/L, Hb < 10 g/dl or platelets < 100 G/L
- Moderate to severe renal insufficiency (GFR < 30 ml/min)
- Severe hypogammaglobulinemia defined as gamma globulins or IgG < 5 g/l
- Reduced hepatic function: AST or ALT > 2x ULN (re-testing is allowed, see section 5.10)
- Prolonged ECG's corrected QT interval (>500 ms)
- Known history of maculopathy
- Patients will be informed of the risk of alcohol consumption and will be recommended to avoid alcohol during the entire study
- Not affiliated to a social security regime (specific for France)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-09-2023
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Arava
Generic name:	Leflunomide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	MYCOPHENOLATE MOFETIL TEVA
Generic name:	MYCOPHENOLATE MOFETIL
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Plaquenil
Generic name:	Hydroxychloroquine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-07-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-12-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-01-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-07-2023

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EU-CTR	CTIS2023-510054-16-00
EudraCT	EUCTR2019-002470-32-NL
CCMO	NL72086.042.21