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Sponsor / Company: Sanofi **Drug substance:** Z0188 (hydroxychloroquine)	**Study Identifiers:** NCT01551069, UTN U1111-1126-8072 **Study code:** EFC12368
Title of the study: A randomized, double blind, baseline controlled study using placebo as reference for assessing the efficacy and safety of hydroxychloroquine sulfate in patients with systemic lupus erythematosus or cutaneous lupus erythematosus in the presence of active lupus erythematosus specific skin lesion	
Study center(s): 22 sites in Japan	
Study period: Date first patient enrolled (date of obtaining consent): 22/Mar/2012 Date last patient completed (Week 55): 30/Apr/2014	
Phase of development: Phase 3	

Objectives:

Primary objective:

- To investigate the efficacy on skin manifestation of 16 weeks treatment of once daily regimen of hydroxychloroquine sulfate (HCQ) in patients with cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) with active skin manifestation (Cutaneous Lupus Erythematosus Disease Area and Severity Index [CLASI] activity score is ≥4 points) concomitant treatment with or without corticosteroid.

Secondary objective:

- To evaluate the efficacy on skin manifestation and the safety of 16 weeks treatment of once daily regimen of HCQ versus placebo as the reference group in patients with CLE and SLE with active skin manifestation (CLASI activity score is ≥4 points) concomitant treatment with or without corticosteroid.
- To investigate the safety of 16 weeks treatment of once daily regimen of HCQ in patients with CLE and SLE with active skin manifestation concomitant treatment with or without corticosteroid.
- To investigate the safety and efficacy of 52 weeks long-term treatment of once daily regimen of HCQ in patients with CLE and SLE.
- To investigate the influences of the dose reduction of corticosteroid on CLE and SLE patients treated with once daily regimen of HCQ with corticosteroid.
- To investigate the efficacy of once daily regimen of HCQ on systemic symptoms, musculoskeletal symptoms and immunological parameters in SLE patients.
- To investigate the change in effectiveness index (skin manifestations and disease activity) and safety after the treatment of HCQ in the follow-up period.
- To calculate the pharmacokinetic parameters by the population pharmacokinetic analyses.

Methodology:

A Phase 3, double-blinded, baseline-controlled, multicenter study.

In this study, the primary objective was a comparison of the efficacy (CLASI activity score) of HCQ on skin lesions before and after HCQ treatment. In addition, a placebo group is also set as the reference group. The subjects were stratified with the baseline CLASI activity score (<9 points, ≥9 points) and randomly assigned to the HCQ (HCQ/HCQ) group and the placebo (placebo/HCQ) group at a ratio of 3 to 1.

- A 16-week double-blind period was set for making the relative evaluation using the placebo group as the reference group for the purpose of securing the objectivity and the evidence level of the efficacy/safety evaluation performed as one of the secondary objectives.
- In the HCQ treatment period set after the double-blind period to investigate the long-term safety and efficacy of once daily regimen of HCQ for up to 52 weeks, a single-blind design was adopted.

* The treatment groups are respectively described as “HCQ group” and “placebo group”, in the double-blind period and respectively as “HCQ/HCQ group” and “placebo/HCQ group” in the other periods.

Number of patients**:**	Planned: About 100 subjects Randomized: 103 subjects (the HCQ [HCQ/HCQ] group: 77 subjects, the placebo [placebo/HCQ] group: 26 subjects) Treated: 103 subjects (the HCQ [HCQ/HCQ] group: 77 subjects, the placebo [placebo/HCQ] group: 26 subjects)
Evaluated:	
	Efficacy: Full Analysis Set (FAS): 96 subjects (the HCQ [HCQ/HCQ] group: 72 subjects, the placebo [placebo/HCQ] group: 24 subjects)
	Safety: 103 subjects (the HCQ [HCQ/HCQ] group: 77 subjects), the placebo [placebo/HCQ] group: 26 subjects)
	Pharmacokinetics: To be reported in the population pharmacokinetic analysis report to be prepared separately

Diagnosis and criteria for inclusion:

Major inclusion criterion:

- Patients diagnosed as CLE.

Major exclusion criteria:

- Patients receiving oral corticosteroid at the equivalent dose of prednisolone more than 15 mg/day, if oral corticosteroid is used.
- Patients with a CLASI activity score of less than 4 points evaluated by a dermatologist at the time of Visit 1 or Visit 2.
- Patients with a change in CLASI activity score of 20% or more from Visit 1 to Visit 2.

Study treatments

Investigational medicinal product(s):

- Tablet containing 200 mg of HCQ (HCQ-200 mg tablet)

Reference product:

- Placebo tablet indistinguishable in appearance from HCQ-200 mg tablet (HCQ-P tablet)

Route(s) of administration: Oral

Dose regimen: Once-daily administration of HCQ 200 to 400 mg (not exceeding 6.5 mg/kg) or placebo

- Ideal body weight: <46 kg
  - One tablet (200 mg) of HCQ or placebo tablets after breakfast
- Ideal body weight: 46 kg to <62 kg
  - One tablet (200 mg) / two tablets (400 mg) of HCQ or placebo tablets after breakfast every other day
- Ideal body weight: ≥62 kg
  - Two tablets (400 mg) of HCQ or placebo tablets after breakfast

Duration of treatment: 52 weeks (placebo: 16 weeks)

Duration of observation:

The duration of the observation period of this study treatment consisted of the following 4 periods, being 59 weeks (413 days) in total.

- Screening period: 4 weeks (±7 days)
  From 4 weeks (±7 days) before Day 1 to Day 1 (prior to registration)
- Double-blind period: 16 weeks (± 7 days)
  From Day 1 to Week 16 (± 7 days)
- Single-blind period: 36 weeks (± 7 days)
  From the next day after 16 weeks (± 7 days) following Day 1 to 52 weeks (± 7 days)
- Post-treatment follow-up period: 3 weeks (+7 days)
  Up to 3 weeks (+7 days) after the last dose of the investigational product

Criteria for evaluation:

Efficacy:

Primary endpoint:

- Change in CLASI activity score form baseline (Visit 2) to Week 16 (Visit 6) after the investigational administration.

Major secondary endpoints:

- Change in CLASI activity score form baseline (Visit 2) to Week 52 (Visit 15). after the investigational administration.
- Global assessment by Investigator (skin and other than skin), global assessment by patients (skin), quality of life (QoL) related to the skin manifestations (Skindex29), central photo evaluation skin manifestations, Routine Assessment of Patient Index Data 3 (RAPID3) (daily life activity, pain associated with the original disease [visual analogue scale (VAS)], severity related original disease by patient [VAS]), Fatigue VAS, British Isles Lupus Assessment Group (BILAG) (systemic and musculoskeletal symptoms), and immunological parameters.
- Dose reduction of concomitant corticosteroid (from Week 16 to Week 55 after the initiation of the treatment).

Safety:

- Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), clinical laboratory data, vital signs.
- Ophthalmologic examinations (visual acuity examination, slit-lamp examination, funduscopic examination, visual field examination, and color vision examination).

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Sampling time:

- Of 4 visits, Visits 11 to 14 (Weeks 36 to Week 48) when the steady state is attained, pharmacokinetic (PK) blood samples will be collected at 3 time points.

- The blood samples were collected at three time points: 3 to 5 hours (around the maximum concentration [C_{max}]), 7 to 11 hours, and 20 to 28 hours (around the trough serum concentration [C_{trough}]) after administration of the investigational medicinal product (IMP).

Analysis method: Liquid chromatography tandem mass spectrometry (LC/MS/MS) method.

Statistical methods:

Primary analysis:

To compare between CLASI activity score at baseline and the corresponding score at Week 16 (Visit 6) using two-sided paired t-test on the HCQ group. When available scores at Visit 6 do not exist, scores will be extrapolated based on the last observation carried forward (LOCF) method.

Secondary analysis:

Efficacy:

Global assessment by Investigator (skin and other than skin), global assessment by patient (skin), QoL of patient related to the skin manifestations (Skindex29), central photo evaluation skin manifestations RAPID3 (daily life activity, pain associated with the original disease [VAS], severity judgment related to the original disease by patient [VAS], total score), malaise VAS, BILAG (systemic and musculoskeletal symptoms), and immunological parameters were summarized in each treatment group. Furthermore, dose reduction of concomitant corticosteroid was summarized in each treatment group.

Safety:

For Safety Analysis Set, adverse events (AEs) during the treatment period are summarized by group. Concerning laboratory test values and vital signs, potentially clinically significant abnormality (PCSA) is summarized by group.

Summary:

Patient disposition:

In this study, 103 subjects were randomized, and the subjects were stratified by the baseline CLASI activity score (<9 points, ≥9 points) and randomly assigned to the HCQ (HCQ/HCQ) group and the placebo (placebo/HCQ) group at a ratio of 3:1 (the HCQ/HCQ group: 77 subjects, the placebo/HCQ group: 26 subjects). All of the randomized subjects were administered the IMP. Among the randomized subjects, 7 subjects (the HCQ/HCQ group: 5 subjects, the placebo/HCQ group: 2 subjects) were excluded from the FAS for reasons such as the absence of an available CLASI activity score after administration of the investigational product, and 96 subjects (the HCQ/HCQ group: 72 subjects, the placebo/HCQ group: 24 subjects) were included in the FAS and analyzed for efficacy.

Among the randomized 103 subjects, 90 subjects (the HCQ/HCQ group: 69 subjects, the placebo/HCQ group: 21 subjects) completed the study period up to 55 weeks after starting the study treatment, and 13 subjects (the HCQ/HCQ group: 8 subjects, the placebo/HCQ group: 5 subjects) discontinued the study treatment during the double-blind or single-blind period. None of the subjects died during the study period up to 55 weeks after starting the study treatment.

The mean baseline CLASI activity score was 13.5 in the HCQ/HCQ group and 13.6 in the placebo/HCQ group. In those subjects complicated with SLE, the mean baseline muscle or joint pain (VAS) score in RAPID3 due to the original disease was 3.15 in the HCQ/HCQ group and 3.25 in the placebo/HCQ group, and the mean baseline RAPID3 total score was 7.14 in the HCQ/HCQ group and 7.93 in the placebo/HCQ group. The mean baseline Fatigue VAS score was 4.07 in the HCQ/HCQ group and 4.63 in the placebo/HCQ group.

In the FAS, there were no marked differences in demographic characteristics and baseline original disease characteristics between the 2 treatment groups.

Efficacy results:

Examining the “Change in CLASI activity score from the baseline (Visit 2) to Week 16 (Visit 6) after the investigational administration” being the primary endpoint, the mean change at Week 16 of this study treatment (LOCF) from the baseline was -4.6 in the HCQ group, showing a statistically significant decrease ($p<0.0001$, paired t-test). On the other hand, also in the placebo group, the mean change from the baseline was -3.2 showing a statistically significant decrease ($p=0.0021$, paired t-test), but the mean change in the placebo group was smaller than that in the HCQ group.

The subjects in whom the CLASI activity score decreased from the baseline by at least 4 points or 20% (the decrease defined as the rough standard for clinical improvement of CLASI activity score) accounted for 65.3% (47/72 subjects) in the HCQ group and 58.3% (14/24 subjects) in the placebo group at Week 16 of this study treatment (LOCF).

In evaluation of the secondary endpoints related to CLASI activity score, examining the time-course changes in the CLASI activity score, revealed that the mean score decreased markedly at Week 8 and Week 16 of this study treatment in the HCQ/HCQ group in comparison with the placebo/HCQ group and decreased thereafter toward Week 52. In addition, among the subjects of the placebo/HCQ group who were administered HCQ, the CLASI activity score decreased from the time point of completing the double-blind period when the investigational medical product was switched from placebo to HCQ (Week 16 of this study treatment), which supports the efficacy results obtained in the HCQ/HCQ group.

In evaluation of the other secondary endpoints related to CLE skin manifestations, on the scale of Skindex29 being the scale for evaluating the subject’s skin-related QoL, all the emotion/symptom/function subscale scores and the total score decreased significantly from the baseline in the HCQ group at Week 16 of this study treatment (LOCF). Moreover in the placebo group, all the scores decreased significantly from the baseline, but the mean changes were smaller than those in the HCQ group. Also in global assessment by Investigator, global assessment by patient and central photo evaluation of skin manifestations, the rate of subjects with an assessment of “Improvement” or better was respectively 51.4% (36/70 subjects), 21.4% (15/70 subjects) and 59.4% (41/69 subjects) in the HCQ group and respectively 8.7% (2/23 subjects), 13.0% (3/23 subjects) and 30.4% (7/23 subjects) in the placebo group at Week 16 of this study treatment (LOCF), being all higher in the HCQ group. In the HCQ/HCQ group, all of the emotion/symptom/function subscale scores and the total score on the scale of Skindex29 were also improved after Week 16 of this study treatment up to Week 52. The rate of subjects with an assessment of “Improvement” or better in central photo evaluation of skin manifestations was also maintained after Week 16 of this study treatment up to Week 52 (59.4% [41/69 subjects] at Week 16, 58.8% [40/68 subjects] at Week 32, 62.7% [42/67 subjects] at Week 52). In both global assessment by Investigator and global assessment by patient of skin manifestations, the rate of subjects with an assessment of “Improvement” or better increased after Week 16 of this study treatment (global assessment by Investigator: 51.4% [36/70 subjects] at Week 16, 64.7% [44/68 subjects] at Week 32, 64.2% [43/67 subjects] at Week 52; global assessment by patient: 21.4% [15/70 subjects] at Week 16, 38.2% [26/68 subjects] at Week 32, 52.2% [35/67 subjects]) at Week 52).

In subgroup analysis of active skin manifestations, the mean change in the CLASI activity score at Week 16 of this study treatment (LOCF) from the baseline in the HCQ group was -2.2 in those subjects with a baseline CLASI activity score less than 9 points and -5.9 in those subjects with a baseline CLASI activity score of not less than 9 points, showing this decrease from the baseline in both the subgroups, and the decrease exceeded the 4-point decrease being the rough standard for clinical improvement of CLASI activity score in those subjects with a baseline CLASI activity score not less than 9 points.

In addition, in all the subgroups of HCQ group related to whether complicated or not complicated with SLE, the disease type of CLE (acute cutaneous lupus erythematosus [ACLE], subacute cutaneous lupus erythematosus [SCLE], and chronic cutaneous lupus erythematosus [CCLE]) and the baseline dosage of corticosteroid (prednisolone equivalency), the mean CLASI activity score decreased at Week 16 of this study treatment (LOCF) from the baseline.

The above results confirmed that the efficacy on skin manifestation of 16 weeks treatment and the long-term efficacy of 52 weeks treatment of once daily regimen of HCQ in patients with CLE (irrespective of whether complicated or not complicated with SLE) with or without concomitant treatment of corticosteroid.

Upon examining the subjects complicated with SLE in the HCQ group, the RAPID3 total score and subscale scores (“muscle or joint pain [VAS] due to the original disease” and “patient’s severity judgment of original disease [VAS]”) were significantly

improved from the baseline at Week 16 of this study treatment. In the placebo group, the changes in these scores from the baseline were small. Also “Fatigue VAS” showed a statistically significant improvement from the baseline at Week 16 of this study treatment (LOCF) in the HCQ group, and the mean score decrease was larger than that in the placebo group. Furthermore, on also looking at BILAG, both general systemic symptoms and musculoskeletal symptoms showed a statistically significant improvement from the baseline at Week 16 of this study treatment (LOCF) in the HCQ group. In the global assessment by Investigator of symptoms other than skin manifestations including overall evaluations of these SLE symptoms, the rate of subjects with an assessment of “Improvement” or better and the rate of subjects with an assessment of “Slight improvement” or better were respectively 47.4% (18/38 subjects) and 68.4% (26/38 subjects) in the HCQ group and respectively 36.4% (4/11subjects) and 54.5% (6/11subjects) in the placebo group, both being higher in the HCQ group. In the HCQ/HCQ group, the RAPID3 total score, “muscle or joint pain (VAS) due to the original disease”, “patient’s severity judgment of original disease (VAS)” and “Fatigue VAS” were also improved after Week 16 of this study treatment up to Week 52, and the BILAG (general systemic symptoms, musculoskeletal symptoms) showed stable changes after Week 16 of this study treatment. The rate of subjects with an assessment of “Improvement” or better in the physician’s global assessment of symptoms other than cutaneous lesions increased after Week 16 of this study treatment (47.4% [13/38 subjects] at Week 16, 43.6% [17/39 subjects] at Week 32, 58.3% [21/36subjects]) at Week 52), and the rate of subjects with an assessment of “Slight improvement” or better showed similar changes (68.4% [26/38 subjects] at Week 16, 64.1% [25/39 subjects] at Week 32, 86.1% [31/36 subjects] at Week 52).

The above results confirmed that the efficacy on skin manifestations of 16 weeks treatment and the long-term efficacy of 52 weeks of treatment of once daily regimen of HCQ in patients with SLE with general systemic symptoms and musculoskeletal symptoms of SLE.

Safety results:

Safety results:

The AEs (by system organ class [SOC]) developed or worsened with a high incidence (not less than 10%) after the first dose of the IMP (TEAEs) in the double-blind period until Week 16 of this study treatment were “Infections and infestations”, “Skin and subcutaneous tissue disorders”, “Gastrointestinal disorders” and “Nervous system disorders” in the HCQ group and “Infections and infestations”, “gastrointestinal disorder”, “Respiratory, thoracic and mediastinal disorders” and “Skin and subcutaneous tissue disorders” in the placebo group. The only TEAE (SOC) developed in the HCQ group with an incidence higher by at least 10% in comparison with the placebo group was “Skin and subcutaneous tissue disorders” (the HCQ group: 29.9% [23/77 subjects], the placebo group: 11.5% [3/26 subjects]). The AEs (by preferred term [PT]) developed with an incidence not less than 5% were “common cold”, “diarrhoea”, “headache” and “urticaria” in the HCQ group and “common cold”, “bronchitis”, and “headache” in the placebo group. The TEAEs (PT) developed in the HCQ group with an incidence higher by at least 5% in comparison with the placebo group were “diarrhoea” and “urticaria”. The adverse reaction (AR) developed with an incidence higher than 5% was only “diarrhoea” developed in the HCQ group (not developed in the placebo group). Almost all of the ARs developed in this study were mild or moderate, and as a severe adverse reaction (SAR), “drug eruption” was developed in 1 subject of the HCQ group, but recovery was observed. As an SAR, “drug eruption” was observed in the HCQ group until Week 16 of this study treatment, but none in the placebo group. As ARs which resulted in discontinuation of this study, “drug eruption”, “toxicodermia” and “generalised eruption” were observed in the HCQ group but not in the placebo group.

The TEAEs (SOC) developed with an incidence not less than 10% in the entire period up to Week 55 (including the 3-week follow-up observation period) were “Infections and infestations”, “Skin and subcutaneous tissue disorders”, “Gastrointestinal disorders”, “Musculoskeletal and connective tissue disorders”, “Injury, poisoning and procedural complications”, “Nervous system disorders”, “Eye disorders” and “General disorders and administration site conditions” in the HCQ/HCQ group and “Infections and infestations”, “Skin and subcutaneous tissue disorders”, “Gastrointestinal disorders”, “Respiratory, thoracic and mediastinal disorders”, “Nervous system disorders”, “Eye disorders”, “Ear and labyrinth disorders”, “Musculoskeletal and connective tissue disorders” and “General disorders and administration site conditions” in the placebo/HCQ group. The TEAEs (PT) developed with an incidence not less than 5% were “common cold”, “diarrhoea”, “back pain”, “bronchitis”, “headache”, “myalgia ”, “paronychia”, “contact dermatitis”, “urticaria”, “gastroenteritis”, “vomiting”, “rash”, “ligament sprain” and “burn” in the HCQ/HCQ group and “common cold”, “headache”, “diarrhoea”, “bronchitis”, “influenza”, “cystitis”, “pharyngitis”, “rhinitis”, “skin papilloma”, “corneal erosion”, “vertigo”, “upper respiratory inflammation” and “fatigue” in the placebo/HCQ group. The only

AR developed with an incidence higher than 5% was “diarrhoea” in both the HCQ/HCQ group and placebo/HCQ group. Almost all of the ARs developed in this study were mild or moderate, and as an SAR, in addition to “drug eruption” developed in the aforementioned one subject of the HCQ/HCQ group, a “hepatic function abnormal” was developed in another subject of the HCQ/HCQ group (single-blind period) and “Stevens-Johnson syndrome” in 1 subject of the placebo/HCQ group (single-blind period), but recovery was seen in all of these cases. These 3 events were all SARs and resulted in discontinuation of the study treatment. As another SAR, “cellulitis” was developed in 1 subject of the HCQ/HCQ group (single-blind period). As other ARs which resulted in discontinuation of the study treatment, “toxicodermia” and “generalised eruption” were developed in the HCQ/HCQ group (double-blind period) and “toxicodermia” in the placebo/HCQ group (single-blind period).

Many of the ARs classified as “Skin and subcutaneous tissue disorders” in SOC appeared within 28 days after starting HCQ administration and all appeared within 56 days after starting HCQ administration.

As the TEAEs related to eye disorders, the events classified as “Eye disorders”, “Infections and infestations” or “Investigations” in the SOC were developed during the entire period up to 55 weeks after starting this study treatment in 14 subjects (19 events) of the HCQ/HCQ group and 4 subjects (5 events) of the placebo/HCQ group. In regards to the “dry eye”, “conjunctivitis”, “chorioretinal atrophy” and “vitreous floater” developed in 1 subject each of the HCQ/HCQ group, it was judged that a causal relationship with the IMP could not be ruled out, but the study treatment was not discontinued and recovery was confirmed for the “dry eye”, “conjunctivitis” and “myodesopsia”. In the case of the “chorioretinal atrophy” developed around the right eye in the examination performed at Week 32 of this study treatment, there were no influences on visual function and the ophthalmologist in charge made a judgment of “progress observation in continuation of the study treatment”, which was also supported by the committee for evaluation of safety of ophthalmologic findings in this study. Thereafter, the study treatment was continued up to Week 52, and no worsening was recognized.

The above results confirmed that favorable tolerability of 16 weeks treatment and the long-term safety of 52 weeks treatment of once daily regimen of HCQ in patients with CLE (irrespective of whether complicated or not complicated with SLE) with or without concomitant treatment of corticosteroid.

Pharmacokinetic results:

To be reported in the population pharmacokinetic analysis report to be prepared separately.

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