A randomised, parallel-group, double-blind, placebo-controlled phase 3 study to Determine the effectiveness of the type I interferon receptor antibody, Anifrolumab, In SYstemic sclerosis: DAISY study design and rationale

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Abstract

Objective

The type I interferon pathway is a promising target for treatment of patients with systemic sclerosis (SSc). Here, we describe the design of a multinational, randomised phase 3 study to Determine the effectiveness of the type I interferon receptor antibody, Anifrolumab, In SYstemic sclerosis (DAISY).

Methods

DAISY includes a 52-week double-blind, placebo-controlled treatment period, a 52-week open-label active treatment period, and a 12-week safety follow-up period. The patient population includes a planned 306 adults with limited or diffuse cutaneous active SSc who satisfied American College of Rheumatology/European Alliance of Associations for Rheumatology 2013 SSc criteria. Use of standard immunosuppressants, including mycophenolate mofetil, at a stable dose prior to randomisation is permitted in addition to weekly subcutaneous anifrolumab or placebo. Efficacy will be assessed at Week 52 via Revised-Composite Response Index in SSc (CRISS)-25 response (primary endpoint). Lung function and skin thickness will be assessed via change from baseline in forced vital capacity in patients with SSc-associated interstitial lung disease and modified Rodnan Skin Score, respectively (key secondary endpoints).

Conclusion

The DAISY trial will evaluate the efficacy and safety of anifrolumab as a first-in-class treatment option for patients with both limited and diffuse cutaneous SSc and will provide insight into the contributions of type I interferon to SSc pathogenesis. Revised-CRISS-25 can account for improvement and worsening in a broad set of validated clinical measures beyond lung function and skin thickness, including clinician- and patient-reported outcomes, capturing the heterogeneity of SSc.

Key words

autoimmune disease, systemic sclerosis, anifrolumab, type I interferon

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Plain language summary

Systemic sclerosis is a chronic autoimmune disease that leads to inflammation and scarring of the skin and internal organs, especially the lungs. Systemic sclerosis and lupus are both associated with increased interferon signalling, which is usually triggered by viral infections, but is related to damaging inflammation in these diseases. Anifrolumab, a drug that blocks interferon signalling, is already used to treat patients with lupus (also known as SLE), so it could potentially be used to treat patients with systemic sclerosis. This publication details the DAISY study design and explains why it is needed.

This study will follow 2 groups of 153 patients with systemic sclerosis over 2 years. During the first year, in addition to any standard immunosuppressant therapy, the groups will receive weekly injections of either anifrolumab or "dummy drug" (placebo). In the second year, all patients will receive anifrolumab with their standard immunosuppressant therapy. Multiple factors will be considered to evaluate the efficacy of anifrolumab treatment, including clinical measurements of skin thickness and lung function, and questionnaires completed by clinicians and patients to report on patient health and their everyday function during treatment.

The DAISY study will investigate the efficacy and safety of anifrolumab treatment in a diverse group of patients with systemic sclerosis who currently have limited options for effective treatment. The study will evaluate the impact of anifrolumab treatment on multiple aspects of the disease, and how patients feel about their overall health-related quality of life.

Introduction

Systemic sclerosis (SSc) is a complex, heterogeneous autoimmune disease in which vasculopathy, inflammation, and fibrosis contribute to damage in multiple organs (1). Dysregulated interferon signalling is a cardinal feature of autoimmune diseases including systemic lupus erythematosus (SLE), Sjögren's syndrome, and SSc (2). There is evidence that type I interferon dysregulation may play an important role in SSc pathogenesis (3). Excess type I interferon signalling has been consistently identified in the blood and tissues in the majority of patients with SSc (4, 5), and the degree of type I interferon pathway activity has been associated with the presence of SSc autoantibodies (6) and the severity of organ involvement (3, 7). Immunoablation and stem cell rescue in patients with SSc was observed to normalise the levels of two interferon gene expression modules; this change in transcriptional levels was significantly correlated with improvement in forced vital capacity (FVC) (8), an important clinical measure of lung function (9).

Particularly strong support for a pathogenic role of type I interferon in SSc came from a randomised, placebo-controlled trial of patients with early diffuse cutaneous SSc, in which treatment with recombinant type I interferon-α led to SSc disease progression rather than the disease improvement that had been anticipated (10). Conversely, inhibition of the type I interferon pathway has demonstrated efficacy in the treatment of SLE, another disease in which the interferon signature has been associated with disease activity (11).

Anifrolumab is a fully-human, IgG1κ monoclonal antibody that targets the type I interferon receptor α subunit 1 (IFNAR1) and blocks downstream type I interferon signalling, which suppresses the interferon gene signature (IFNGS) (12-14). Following phase 3 trials, anifrolumab was approved for use in patients with moderate to severe SLE in multiple countries (14-19); the use of anifrolumab in patients with SLE is supported by 4 years of safety data (20).

The safety/tolerability, pharmacodynamics, and pharmacokinetics of anifrolumab were previously investigated in a phase 1 trial of patients with SSc (21). This study revealed an adequate safety and tolerability profile of anifrolumab in patients with SSc, whereby most treatment-emergent adverse events were mild or moderate, and anifrolumab treatment decreased type I IFNGS expression in whole blood and skin (21). IFNAR1 blockade was also associated with suppression of T-cell activation markers and collagen accumulation, suggesting the potential benefit of ani-

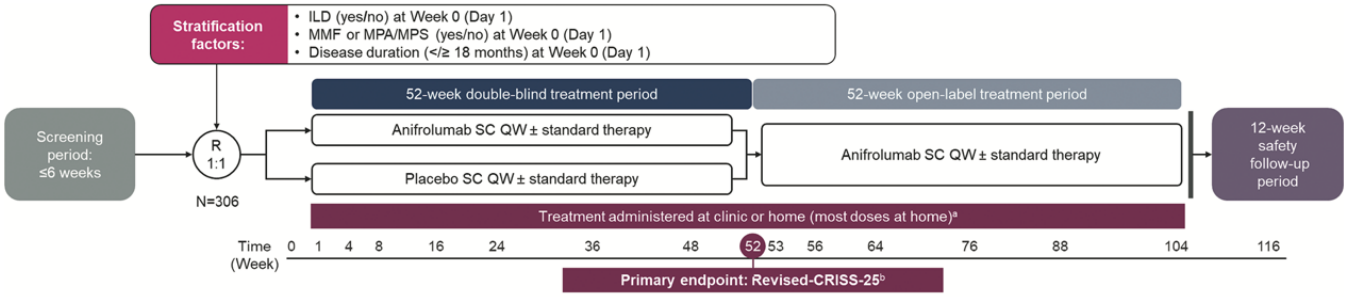

Fig. 1. Study design.
Figure originally published in Khanna D *et al*.: *J Scleroderma Relat Disord* 2024; 9(Supplement): 61-395 (39).
The DAISY study will include adults with limited or diffuse cutaneous active SSc who were ≤6 years from their first non-Raynaud's manifestation of the disease. Patients are permitted to take standard immunosuppressant therapy (hydroxychloroquine, MMF, MPA/MPS, methotrexate, azathioprine, tacrolimus, or oral glucocorticoids) in addition to randomized treatment. A group of 15 patients with SSc in the United States and the United Kingdom were consulted on study design, visit schedule, self-administration dosing, and visit procedures/activities.
[a]The last dose of study intervention will be administered at Week 51 in the double-blind treatment period and at Week 103 in the open-label treatment period; Week 52 is a shared visit between the double-blind treatment period (procedures) and the open-label treatment period (study drug administration);
[b]Revised version of the 2-step ACR-CRISS algorithm.
ACR: American College of Rheumatology; CRISS: Composite Response Index in Systemic Sclerosis; DAISY: Determine the effectiveness of the type I interferon receptor antibody, Anifrolumab, In SYstemic sclerosis; MMF: mycophenolate mofetil; MPA/MPS: mycophenolic acid or mycophenolate sodium; QW: once weekly; R: randomisation; SC: subcutaneous; SSc: systemic sclerosis.

frolumab for targeting tissue fibrosis, a hallmark of SSc pathology (22).
Together, the strong evidence for the role of type I interferon in SSc pathogenesis and the safety and efficacy results from the phase 1 trial in patients with SSc support further investigation of anifrolumab as a treatment for SSc (3, 21, 22). Thus, here we report the study design of a multinational, randomised, placebo-controlled, double-blind phase 3 study (DAISY; NCT05925803). DAISY aims to evaluate the efficacy of subcutaneous (SC) anifrolumab in adult patients with SSc who may be taking one or a combination of protocol-specified standard therapies and to establish a safety profile of anifrolumab treatment in SSc.

Methods

Study design

DAISY is a multinational, randomised (1:1), parallel-group, double-blind, placebo-controlled, phase 3 study that is planned to include 306 patients. The study includes 17 study visits over 4 periods with a total study duration of ~122 weeks: a ≤6-week screening period prior to randomisation; a 52-week double-blind, placebo-controlled treatment period; a 52-week open-label active treatment period; and a 12-week safety follow-up period (Fig. 1). The primary and key secondary endpoints will be evaluated at Week 52. The open-label treatment period will allow for the observation of treatment effects beyond 1 year. Patient input contributed to the design of the study.

Ethics

The study is designed to be conducted in accordance with consensus ethical principles derived from international guidelines, including the Declaration of Helsinki as amended in October 2013. The study protocol, any amendments, Investigator's Brochure, and informed consent forms will be reviewed and approved by an Institutional Review Board/Ethics Committee for each study site, and patients will provide informed consent prior to participation.

Patient selection

DAISY will include adults 18–70 years of age (inclusive) with SSc (disease duration within 6 years from first non-Raynaud's phenomenon manifestation) according to 2013 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria for SSc (23), and either limited or diffuse cutaneous subset as defined by LeRoy and Medsger (24). Use of standard immunosuppressants, including hydroxychloroquine, methotrexate, azathioprine, mycophenolate mofetil (MMF), mycophenolic acid or mycophenolate sodium (MPA/MPS), tacrolimus, or oral glucocorticoids, will be permitted (not required) at a stable dose prior to randomisation; the dose should remain stable throughout the study. Key inclusion and exclusion criteria are presented in Table I.

Treatment

During the 52-week double-blind period, study participants will receive once-weekly treatment with anifrolumab, administered subcutaneously via an accessorised prefilled syringe (0.8 mL fill volume), or matching placebo. During the 52-week open-label period, all participants will receive once-weekly treatment with anifrolumab, administered subcutaneously. Study intervention may be administered by study staff, patient, or caregiver, in the clinic or, for weekly doses in between clinic visits, at home.

Efficacy assessments

Study objectives and endpoints are outlined in Table II and endpoint definitions are included in Table III.
The primary efficacy endpoint will be Revised-Composite Response Index in SSc (CRISS)-25 (Revised-CRISS-25) response (yes/no) at Week 52 (25). Revised-CRISS-25 uses a 2-step algorithm, with equal weighting given to each of the five validated core measures (modified Rodnan skin score [mRSS], percent predicted forced vital capacity [ppFVC], Health Assessment Questionnaire-Disability Index [HAQ-DI], and patient and clinician global assessments [PtGA and CGA]) (25, 26) and assesses percent improvement and worsening

Table I. Key inclusion and exclusion criteria.

Inclusion criteria
Demographic characteristics
Adult patients from 18 to 70 years of age inclusive
Disease characteristics
SSc according to 2013 ACR/EULAR classification criteria
Limited or diffuse cutaneous subsets according to LeRoy and Medgser
SSc disease duration within 6 years from first non-Raynaud's phenomenon manifestation at the time of signing the ICF
Either HAQ-DI score ≥0.25 points or PtGA score ≥3 points
mRSS >10 with disease duration <18 months and/or lung involvement (ILD) as defined by the protocol, OR
If disease duration ≥18 months and patient does not have ILD, mRSS must be ≥15 with active disease at screening with at least one of the following: 1) C-reactive protein ≥0.6 mg/dL that is unrelated to other conditions or erythrocyte sedimentation rate ≥28 mm/hr or platelet count ≥330×10^9/L; 2) new skin involvement or skin progression by mRSS ≥3 units compared with recent assessments performed within the previous 6 months; or 3) presence of at least one tendon friction rub documented in medical records within the previous 3 months of screening or at screening
Background therapies
Stable background therapies can be used including hydroxychloroquine (≤400 mg/day), methotrexate (≤25 mg/week), azathioprine (≤200 mg/day), MMF (≤3 g/day), MPA/MPS (≤2.16 g/day), oral glucocorticoids (≤10 mg/day prednisone or equivalent), or tacrolimus (≤0.2 mg/kg/day)*
Sex and contraceptive/barrier requirements
Women of childbearing potential with a negative urine pregnancy test
Other criteria
Uninvolved or mildly thickened skin at injection sites
Informed consent
Exclusion criteria
Anticentromere antibody seropositivity on central laboratory
History of SSc renal crisis within past 12 months or eGFR<45 mL/min/1.73 m^2
Overlap syndromes, systemic lupus erythematosus with anti-dsDNA antibody seropositivity or anti-citrullinated protein antibodies-positive rheumatoid arthritis, or SSc mimics (*e.g.* scleromyxedema, eosinophilic fasciitis)
History of, or current, other inflammatory diseases (*e.g.* inflammatory bowel disease, skin disease) that, in the opinion of the investigator, could interfere with efficacy and safety assessments or require immunomodulatory therapy
Evidence of moderately severe concurrent nervous system, renal, endocrine, hepatic, or gastrointestinal disease (*e.g.* clinical signs of malabsorption or needing parenteral nutrition) not related to SSc, as determined by the investigator
Pulmonary disease with FVC ≤50% predicted, DL_{CO} haemoglobin corrected ≤45% predicted, or airway obstruction (pre-bronchodilator FEV1/FVC <0.7) at screening
Evidence of other severe pulmonary disease as determined by the investigator (*e.g.* asthma requiring biologic therapy, chronic obstructive pulmonary disease requiring long-term, at-home oxygen)
Cardiovascular disease with significant arrhythmia, congestive heart failure (NYHA Class II-IV), unstable angina, uncontrolled hypertension, cor pulmonale, symptomatic pericardial effusion, or cardiac abnormality such as left ventricular failure with ejection fraction <50%
Significant pulmonary hypertension
Haematopoietic stem cell transplantation or solid organ/limb transplantation
Any severe case of herpes zoster infection as defined by the protocol
Known malignancy or a history of malignancy within 5 years, with exception of excised/cured local basal or squamous cell carcinoma of the skin or cervical cancer *in situ*
Major surgery within 8 weeks prior to and/or during study enrolment
Known active current or history of recurrent infections
Any condition that, in the opinion of the investigator or AstraZeneca, would interfere with the efficacy or safety evaluation of the study intervention or put participant at safety risk

*If their doses remained stable for ≥3 months prior to randomization, patients are permitted to have used MMF or MPA/MPS, azathioprine, methotrexate, or tacrolimus in combination with hydroxychloroquine and/or low-dose oral glucocorticoids (≤ 10 mg/day prednisone or equivalent). Patients receiving low-dose glucocorticoids must have maintained a stable dose for ≥2 weeks prior to randomisation. Combinations of MMF, MPA/MPS, azathioprine, methotrexate, or tacrolimus with each other or with other conventional immunosuppressants are not permitted.

ACR: American College of Rheumatology; anti-dsDNA: anti-double-stranded DNA; DL_{CO}: diffusing capacity of the lung for carbon monoxide; eGFR: estimated glomerular filtration rate; EULAR: European Alliance of Associations for Rheumatology; FVC: forced vital capacity; HAQ-DI: Health Assessment Questionnaire-Disability Index; ICF: informed consent form; ILD: interstitial lung disease; MMF: mycophenolate mofetil; MPA/MPS: mycophenolic acid or mycophenolate sodium; mRSS: modified Rodnan Skin Score; NYHA: New York Heart Association; PtGA: Patient's Global Assessment.

in these measures in patients with SSc (Fig. 1). Significant SSc-related events are adjudicated according to the following definitions in Step 1: Renal) new onset scleroderma renal crisis; interstitial lung disease [ILD]) new decline in ppFVC ≥15% (relative to baseline assessment) in new or established ILD and new ppFVC <80% predicted; heart) new onset left ventricular failure (left ventricular ejection fraction ≤45%) requiring treatment; cardiopulmonary) new onset pulmonary arterial hypertension on right heart catheterisation requiring treatment; gastrointestinal) new significant dysmotility requiring enteral (such as nasogastric, jejunostomy, or gastric tube) or parenteral nutrition except for oral supplements; or digital ischaemia) new gangrene, amputation, or unscheduled hospitalisation due to

Table II. Study objectives and endpoints.

Objective	Endpoints
Primary	
To demonstrate the superiority of anifrolumab compared with placebo with or without standard therapy on measures of signs, symptoms, and impacts associated with SSc	Revised-CRISS-25 response at week 52 Where a responder is defined as a patient who meets all of the following criteria: • Improvement in at least two components: ≥5% increase for ppFVC and/or ≥25% decrease for mRSS, HAQ-DI, PtGA, CGA • Worsening in no more than one component: ≥5% decrease for ppFVC and/or ≥25% increase for mRSS, HAQ-DI, PtGA, CGA • No significant SSc-related event [a] Otherwise, a patient is a non-responder
Key secondary	
To demonstrate the superiority of anifrolumab to placebo with or without standard therapy on lung function in patients with SSc-associated ILD	Change from baseline in FVC (mL) at week 52
To demonstrate the superiority of anifrolumab to placebo with or without standard therapy on skin thickness in patients with SSc	Change from baseline in mRSS at week 52
Secondary	
To assess the effect of anifrolumab compared with placebo with or without standard therapy on each component of the measures of signs, symptoms, and impacts associated with SSc included in the Revised-CRISS-25 response	Improvement in each component (evaluated separately) of the Revised-CRISS-25 at week 52, where a responder is defined as follows: • ppFVC ≥5% increase • mRSS ≥25% decrease • HAQ-DI ≥25% decrease • PtGA ≥25% decrease • CGA ≥25% decrease Otherwise, a participant is a non-responder for the component
To assess the effect of anifrolumab compared with placebo with or without standard therapy on ILD progression as quantified by CT in patients with SSc	Change from baseline at week 52 in CT measures of interstitial lung disease (Quantitative ILD, Quantitative light-induced fluorescence)
To assess the effect of anifrolumab compared with placebo with or without standard therapy on skin-specific HRQoL assessment in patients with SSc	Change from baseline in SSPRO at week 52
To assess the effect of anifrolumab compared with placebo with or without standard therapy on lung function in patients with SSc	Change from baseline in ppFVC at week 52 Change from baseline in FVC (mL) at week 52
To assess the effect of anifrolumab compared with placebo with or without standard therapy on lung function in patients with SSc-associated ILD	Change from baseline in ppFVC at week 52
To evaluate the pharmacokinetics, pharmacodynamics, and immunogenicity of SC anifrolumab	Anifrolumab concentration and pharmacokinetic parameters, anti-drug antibodies, and type I interferon 21-gene signature from blood Anti-drug antibody presence and titre during treatment and follow-up Relationships between development of anti-drug antibodies and efficacy, safety, or pharmacokinetic outcome measures

[a] Patient is considered to have a significant SSc-related event, irrespective of improvement in other core components, if they develop any one of the following during the study as defined in Step 1: (1) Renal: new scleroderma renal crisis; (2) ILD: new decline in ppFVC ≥15% (relative to baseline assessment) in new or established ILD and new ppFVC below 80% predicted; (3) Heart: new onset of left ventricular failure (defined as LVEF ≤45%) requiring treatment; (4) Cardiopulmonary: new onset of PAH on right heart catheterisation requiring treatment; (5) Gastrointestinal: new significant dysmotility requiring enteral or parenteral nutrition except for oral supplements; (6) Digital ischaemia: new gangrene, amputation or unscheduled hospitalisation due to worsening of digital ischaemia (*e.g.* due to infection, increasing number of digital ulcers, worsening of established digital ulcers, or surgery), not including scheduled prostacyclin infusions.

CGA: clinician's global assessment; FVC: forced vital capacity; HAQ-DI: Health Assessment Questionnaire-Disability Index; HRQoL: health-related quality of life; ILD: interstitial lung disease; mRSS: modified Rodnan skin score; ppFVC: percent predicted FVC; PtGA: Patient's Global Assessment; Revised-CRISS-25: Revised-Composite Response Index in SSc Score; SSc: systemic sclerosis; SSPRO: Scleroderma Skin Patient Reported Outcome.

worsening of digital ischaemia (*e.g.* due to infection, increasing number of digital ulcers, worsening of established digital ulcers, or surgery), not including scheduled prostacyclin infusions. Irrespective of improvement in other core components, patients that develop Step 1 events during the study are classified as non-responders. In patients with no new or worsening major organ involvement, a Revised-CRISS-25 response is determined in Step 2: response is achieved by showing improvement in ≥2 components and worsening in ≤1 component of the measure. Improvement and worsening thresholds were defined according to published minimal clinically important differences for each measure: a ≥25% change in mRSS, HAQ-DI, CGA, or PtGA, or a ≥5% change in ppFVC (25).

Table III. Definitions of assessments used in the DAISY study.

Assessment	Abbreviation	Definition
Revised-Composite Response Index in SSc Score*	Revised-CRISS-25	A composite endpoint where a responder is defined as a patient who shows improvement in at least 2 components (≥5% increase for ppFVC and/or ≥25% decrease for mRSS, HAQ-DI, PtGA, CGA) and worsening in no more than one component (≥5% decrease for ppFVC and/or ≥25% increase for mRSS, HAQ-DI, PtGA, CGA) with no significant SSc-related event over the duration evaluated; otherwise, a patient is a non-responder
Forced Vital Capacity†	FVC	Assessed with a spirometer according to ATS/ERS 2019 guidelines (40)
Modified Rodnan Skin Score†	mRSS	Patient's skin thickness is rated by clinical palpation using a 0–3 scale (0=normal skin; 1=mild thickness; 2=moderate thickness; 3=severe thickness with inability to pinch the skin into a fold) for each of 17 surface anatomic areas of the body: face, anterior chest, abdomen, and fingers, forearms, upper arms, thighs, lower legs, dorsum of hands and feet with right and left considered separately. Individual values are added and the sum is defined as the total skin score (41)
Health Assessment Questionnaire–Disability Index	HAQ-DI	20-item instrument with which a patient scores their difficulties in performing activities of daily living over the last week in each of 8 sections (Dressing, Arising, Eating, Walking, Hygiene, Reach, Grip, and Activities) from 0 ("Without Any Difficulty") to 3 ("Unable to Do"). The overall score is determined by summing the highest item score in each section and dividing by 8. The Standard Disability Index will be used to adjust the score for each category based on the use of an aid, device, or assistance (42)
Patient's Global Assessment	PtGA	11-point numerical rating scale used for patient to report their overall health in the last week from 0 ("Excellent") to 10 ("Extremely Poor")
Clinician's Global Assessment	CGA	Physician assesses patient's overall health in the last week from 0 ("Excellent") to 10 ("Extremely Poor"), with an option to choose "Not Known" if the patient is new to the clinic
Scleroderma Skin Patient Reported Outcome	SSPRO	18-item instrument with 4 domains (Physical Effects, Physical Limitations, Emotional Effects, and Social Effects). Patient reports skin-related HRQoL over the last 4 weeks using a 7-point numerical rating scale from 0 ("Not at All") to 6 ("Very Much"), with lower score indicating higher skin-related HRQoL (43)

*The primary objective, to demonstrate the superiority of anifrolumab to placebo with or without standard therapy in SSc, was evaluated using Revised CRISS-25 response at Week 52. Improvements in each component of Revised-CRISS-25 at Week 52 were evaluated separately as secondary objectives;
†One key secondary objective, to demonstrate the superiority of anifrolumab to placebo with or without standard therapy on lung function in patients with SSc-associated ILD, was evaluated using change from baseline in FVC (mL) at Week 52. The other key secondary objective, to demonstrate the superiority of anifrolumab to placebo with or without standard therapy on skin thickness in patients with SSc, was evaluated using change from baseline in mRSS at Week 52.
ATS/ERS: American Thoracic Society/European Respiratory Society; HRQoL: health related quality of life; ILD: interstitial lung disease; ppFVC: percent predicted forced vital capacity; SSc: systemic sclerosis.

Key secondary endpoints include change from baseline to Week 52 in 1) FVC (mL) in patients with SSc-associated ILD and 2) in mRSS in the full analysis dataset. Other secondary endpoints are listed in Table II.

Safety assessments

Safety and tolerability will be evaluated in terms of adverse events (AEs; number and percentage of patients reporting that event, and number of events where appropriate, for each treatment group by system organ class and preferred term), AEs of special interest (serious non-opportunistic infection, opportunistic infection, herpes zoster, tuberculosis [including latent tuberculosis], malignancy, injection site reaction, and major adverse cardiovascular events), vital signs, clinical laboratory tests, 12-lead electrocardiograms, physical examination, Columbia Suicide Severity Rating Scale (C-SSRS), and Patient Health Questionnaire Depression Scale (PHQ-8). Patients will be assessed for coronavirus disease-2019 at each clinic visit.

Pharmacodynamics and pharmacokinetics

Whole blood will be collected at screening and pre-dose for pharmacodynamic, pharmacokinetic, and/or immunogenicity tests throughout the study. The suppression of the type I interferon 21-gene signature in peripheral blood as a percent of baseline will be assessed as a secondary endpoint to follow the biologic effect of anifrolumab on IFNAR1 throughout the study (27). A dichotomous 4-gene IFNGS test in peripheral blood will be used to measure the mRNA overexpression of type I interferon-inducible genes at baseline to evaluate if the participants had high/low IFNGS at study entry (12). This information will be used as part of an exploratory analysis to understand if interferon activity at baseline would impact clinical outcomes. In

addition, whole blood, serum, plasma, and optional skin biopsy samples will be collected for biomarker measurement to explore the wider mechanism of action of anifrolumab.

Statistical methods

Approximately 460 patients will be screened to achieve 306 eligible patients for randomisation. A sample size of 153 participants per arm yields 90% power to detect a treatment difference of 18% in the proportions of patients who achieve revised-CRISS-25 response at week 52 between anifrolumab and placebo groups (two-sided α=0.05). The assumed proportion of responders (participants achieving Revised-CRISS-25 at Week 52) is 30% in the placebo group (25).

Efficacy analyses will be performed using the "full analysis dataset" of all patients who were randomised to treatment and received ≥1 dose of study intervention, or in the patients in the full analysis dataset with SSc-associated ILD. To control for study-wise Type I error, the primary endpoint will be tested at a 2-sided α=0.05 and, if statistically significant, then key secondary endpoints will be tested using a hierarchical sequential testing strategy in pre-defined order.

The proportions of patients achieving Revised-CRISS-25 response at Week 52 with anifrolumab *versus* placebo (the primary endpoint) will be compared using a Cochran-Mantel-Haenszel (CMH) approach, controlling for randomisation stratification factors (ILD [yes/no] at Week 0/Day 1; MMF or MPA/MPS use [yes/no] at Week 0/Day 1; and disease duration from first non-Raynaud's symptom attributable to SSc [</≥18 months] at Week 0/Day 1). Patients were considered non-responders if they received restricted medication, discontinued investigational product, or died prior to Week 52.

To compare treatment groups and assess key secondary endpoints for change from baseline to Week 52 in mRSS, models for repeated measures will include baseline value, treatment group, visit, treatment x visit interaction, and randomisation stratification factors. Models for change from baseline in FVC (mL) will include only randomisation stratification factors MMF or MPA/MPS use at Week 0/Day 1 and disease duration at Week 0/Day 1. Multiple imputation, penalising based on poorest responses observed on placebo to reflect treatment failure, will be used for patient who received restricted medication, discontinued investigational product, or died prior to Week 52.

A "safety dataset" consisting of all patients who received ≥1 dose of study intervention will be used to assess safety and tolerability. Patients' results will be reported according to the treatment actually received.

Discussion

There is strong evidence for a role of type I interferon in the pathogenesis of SLE, SSc, and related connective tissue diseases (3, 7, 8, 10). Multiple lines of evidence support that type I interferon receptor inhibition with anifrolumab has the potential to be a first-in-class treatment option for patients with SSc (21, 22). Here, we describe the design of a multinational phase 3 study to evaluate the safety and efficacy and the long-term treatment profile of anifrolumab in adult patients with diffuse or limited cutaneous SSc.

The study partnered with 15 patients from the United States and United Kingdom living with SSc to capture the patient voice in the study design. Overall, patients perceived the study to be well-designed, and contributed ideas to reduce the burden of the trial and to make it fit-for-purpose for the SSc patient population. Discussions with patients also allowed us to better understand how to capture diaries and PRO instruments and how to mitigate SSc-related issues with using touchscreen digital devices. Patients will be completing several PRO instruments throughout the trial (including the HAQ-DI and PtGA that are components of the primary endpoint); an optional questionnaire will be made available at the beginning, middle, and end of the study, providing further opportunities to capture the patient voice throughout the drug development process and encourage patient feedback regarding their clinical study experience. Furthermore, including the open-label treatment period would provide longer-term safety data for patients with SSc and give patients randomised to placebo during the double-blind period the opportunity to receive active treatment.

A unique feature in the study design is the selection of Revised-CRISS-25 as the primary endpoint in this study, rather than skin or lung assessments alone, which do not adequately capture multiorgan disease activity (28). Use of a composite response measure can provide insights into changes in multiple organ systems, not just skin or other organ involvement (28), and therefore provide insights into overall patient health for a population of patients with a complex, heterogenous systemic disease. Revised-CRISS was recently developed and is being utilized in current phase 2 trials in patients with SSc (belimumab, rituximab, and MMF: NCT03844061; tulisokibart: NCT05270668; BI 685509: NCT05559580) and upcoming phase 3 studies. Revised-CRISS assesses new or meaningful worsening of internal organ involvement and measures the signs, symptoms, and impacts associated with SSc from the patient's and clinician's perspectives by incorporating multiple PROs, clinician-reported outcomes, and surrogate assessments of disease activity (25). Revised-CRISS is derived from ACR-CRISS, with revisions to ensure equal weighting of the core set variables and to limit the floor/ceiling effects seen with that measure (25, 26). Selection of the Revised-CRISS-25 threshold (which translates to improvement of 25% in mRSS, HAQ-DI, PGA, and CGA and improvement of 5% in ppFVC) was based on published minimal clinically important differences in patients with different rheumatic diseases, including SSc (25). The use of the Revised-CRISS-25 composite response enables inclusion of a broad population of patients with SSc, which is a strength of this study.

Whereas randomised SSc trials intending to treat overall SSc activity and skin fibrosis tend to include only patients with diffuse cutaneous SSc (28), this

study includes patients with limited or diffuse cutaneous SSc, which reflects the real-world target population of the therapy. Given that type I interferon might contribute to SSc pathogenesis across multiple different organs (29, 30), it is important to include a broad population of patients in this trial of anifrolumab. Type I interferon, measured as an elevated IFNGS, has been identified at the earliest phases of SSc, and in patients with both limited and diffuse cutaneous SSc (31). Interferon-regulated gene expression has been implicated as a pathogenic pathway in patients with SSc-related ILD (29), and progression of ILD can be similar in patients from both cutaneous subsets (32). In this trial, we will quantify the degree of total lung involvement and fibrosis at baseline and at the end of the trial. Importantly, few treatment options are available for patients with limited cutaneous SSc; as such, new clinical trials are needed in this patient population (33).

Another important feature of the DAISY study design is that patients are permitted to receive background treatment with standard immunosuppressants alongside the trial intervention. MMF is the most common first-line standard therapy for patients with diffuse SSc (28, 34, 35); however, MMF has the potential to confound treatment responses. The option for background immunosuppressive treatment may, for example, reduce the frequency of Step 1 events in the determination of revised/ACR-CRISS response. The randomised, parallel-group SLS-II study evaluated the effects of MMF treatment for 24 months on lung function, compared with oral cyclophosphamide treatment for 12 months, in patients with SSc and symptomatic ILD (36). Though both treatment groups eventually had a similar overall maximum response, ppFVC increased earlier in patients receiving MMF (at 6–9 months) than with cyclophosphamide (34, 36). In the RESOLVE-1 trial, patients were permitted to continue established treatment with stable doses of concomitant immunosuppressives (defined as no dose increases within 8 weeks prior to screening) alongside study drug (lenabasum), and approximately half of patients received MMF (35). Though this inclusive design facilitated timely enrolment (37, 38), treatment with MMF was associated with greater improvement in ACR-CRISS score, change in mRSS, and change in ppFVC, compared with no MMF background immunosuppressant therapy (35).

The potential confounding effect of background MMF on treatment response could be mitigated by the requirement in the DAISY trial for MMF treatment to have been initiated ≥6 months prior to randomisation and at a stable dosage ≤3 g/day for ≥3 months prior to randomisation, in addition to including MMF use as a stratification factor for randomisation. While it could be considered a risk of the study design, including MMF as a background therapy will allow DAISY to provide meaningful information to treating clinicians managing SSc (*e.g.* rheumatologists, dermatologists, and pulmonologists) who wish to understand the role of anifrolumab alongside frequently prescribed standard therapies.

To conclude, DAISY is the first phase 3 trial to investigate a first-in-class IFNAR1 antibody in patients with both diffuse and limited cutaneous SSc. The study design was informed by patients and utilises a composite endpoint that incorporates assessments of how patients feel and function along with clinical disease activity assessments. As it includes a broad patient population, permits the use of standard therapy, and spans a 2-year on-drug period, DAISY will be able to provide important insights into the potential of anifrolumab for SSc treatment.

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Competing interests

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C. Kleoudis is employee of AstraZeneca.

J. Xu, E. Csomor, C. Seo, M. Albulescu, R. Tummala and R.N. Kalyani are employees and shareholders of AstraZeneca.

H. Al-Mossawi has role of leadership or fiduciary role at Immunocore; a formerly a full-time employee of AstraZeneca, and holds stock or stock options from AstraZeneca and Immunocore.

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