Table 1. Spearman Rho Correlation between timed function tests and MMT8, FI-2, patient and physician VAS

	Δ 30s rise from chair test	Δ 30s arm lift test	Δ 2min walk test
Δ MMT8	0.382	0.337	0.724**
Δ FI-2			
Hip flexion right	0.388	0.413	0.314
Hip flexion left	0.503*	0.416	0.422
Neck flexion	0.600**	0.590**	0.610**
Shoulder flexion right	0.183	0.300	0.239
Shoulder flexion left	0.393	0.222	0.207
Shoulder abduction right	0.236	0.222	0.348
Shoulder abduction left	0.182	0.236	0.273
Step test right	0.744**	0.489*	0.326
Step test left	0.840	0.500*	0.378
Heel rise	0.442	0.294	0.388
Toe rise	0.446	0.291	0.419
Δ Physician VAS	-0.508*	-0.506**	-0.215
Δ Patient VAS	-0.600**	-0.597**	-0.249

Δ → change from baseline to 3 months * → Correlation is significant at the 0.05 level ** → Correlation is significant at the 0.01 level

Conclusion: Timed function tests correlated well with MMT 8 and parameters with in FI-2. Thus these tests are good alternatives in assessing disease activity and response assessment in inflammatory myositis.

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SAT0315

INHIBITION OF MICROSOMAL PROSTAGLANDIN E SYNTHASE-1 (mPGES-1) BY GS-248 REDUCES PROSTAGLANDIN E2 BIOSYNTHESIS WHILE INCREASING PROSTACYCLIN IN HUMAN SUBJECTS

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Background: Microsomal prostaglandin E synthase-1 (mPGES-1) catalyzes the formation prostaglandin (PG) E₂ from cyclooxygenase derived PGH₂^(1,2). Inhibition of mPGES-1 leads to reduction of pro-inflammatory PGE₂, while in vessels there is a concomitant increase of vasoprotective prostacyclin (PGI₂) via shunting of PGH₂^(3,4). Apart from relieving symptoms in experimental animal models of inflammation, inhibitors of mPGES-1 cause relaxation of human medium sized arteries⁽⁴⁾ and resistance arteries⁽⁵⁾. The prostaglandin profile following mPGES-1 inhibition, explains the anti-inflammatory effects and also opens for the possibility of treating inflammatory diseases with concomitant vasculopathies. GS-248 is a potent and selective inhibitor of mPGES-1 exhibiting sub-nanomolar IC₅₀ in human whole blood *ex vivo*.

Objectives: To evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of GS-248.

Methods: Healthy males and females (age 18–73 years) were included in the study. Six cohorts were administered single oral doses of 1-300mg GS-248 (n=36) or placebo (n=12), three cohorts were administered once daily doses of 20-180mg GS-248 (n=18) or placebo (n=12) over ten days. In addition, 8 subjects were treated in a separate cohort with 200mg celecoxib bid for ten days. Blood samples were drawn for measurement of GS-248 exposure and production of PGE₂ after LPS incubation *ex vivo*. The content of PGE₂ and PGI₂ metabolites was measured in urine. All analyses were performed by LC-MS/MS.

Results: GS-248 was safe and well tolerated at all tested dose levels. Maximum plasma concentration was achieved 1 - 2.5 hours after dosing, and half-life was

about 10 hours. Induced PGE₂ formation *ex vivo*, catalyzed by mPGES-1, was completely inhibited for 24 hours after a single low dose (40mg) of GS-248. In urine, GS-248 dose-dependently reduced the excretion of PGE₂ metabolite by more than 50% whereas the excretion of PGI₂ metabolite increased more than twice the baseline levels. In the celecoxib cohort urinary metabolites of both PGE₂ and PGI₂ were reduced with approx 50%.

Conclusion: GS-248 at investigated oral doses was safe and well tolerated. There was a sustained inhibition of LPS induced PGE₂ formation in whole blood. In urine, there was a metabolite shift showing reduced PGE₂ and increased PGI₂, while celecoxib reduced both PGE₂ and PGI₂ metabolites. This suggests that selective inhibition of mPGES-1 results in systemic shunting of PGH₂ to PGI₂ formation, leading to anti-inflammatory and vasodilatory effects, while preventing platelet activation. The results warrant further evaluation of GS-248 in inflammatory conditions with vasculopathies such as Digital Ulcers and Raynaud's Phenomenon in Systemic Sclerosis.

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SAT0316

ANTI-PM/SCL ANTIBODIES IN SYSTEMIC SCLEROSIS: CLINICAL ASSOCIATIONS IN THE RESCLE COHORT

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Background: Anti-PM/Scl antibodies are associated to systemic sclerosis (SSc) but are not specific to SSc. The true prevalence of anti-PM/Scl antibodies in SSc is unknown, ranging from 2.5% to 12.5%. An association between anti-PM/Scl antibodies with muscular involvement, pulmonary fibrosis, calcinosis, and a relatively benign prognosis have been described.

Objectives: To compare the clinical manifestations and prognosis of SSc patients according the presence of anti-PM/Scl antibodies in the cohort of RESCLE (Spanish Scleroderma Registry).

Methods: From the Spanish Scleroderma Study Group database, we selected patients in whom anti-PM/Scl antibodies had been tested. We compared demographic features, clinical manifestations, laboratory characteristics, and survival data between patients according the anti-PM/Scl antibodies status.

Results: 72 out of 947 (7%) patients tested positive for anti-PM/Scl antibodies. As presenting SSc manifestations, patients with anti-PM/Scl antibodies had higher prevalence of puffy fingers (11% versus 2%; p=0.002) and arthralgias (11%

versus 4%; $p=0.03$), and lower prevalence of Raynaud's phenomenon (65% versus 82%, $p=0.002$). Regarding cumulative manifestations, myositis (51% versus 15%; $p<0.001$), arthritis (43% versus 22%; $p=0.001$), and interstitial lung disease (ILD) (60% versus 45%, $p=0.014$) were more prevalent in patients with anti-PM/Scl antibodies. In fact, those patients with anti-PM/Scl antibodies presented with FVC ($77.4\% \pm 23.1\%$ versus $85.8\% \pm 23.1\%$; $p=0.006$) and more severe ILD defined as FVC $<70\%$ (41% versus 24%; $p=0.004$). Death rate was similar in patients with and without PM/Scl antibodies (18% versus 17%; $p=0.871$). We did not find differences in terms of death rate nor in the causes of death (SSc and non-SSc related) according to the anti-PM/Scl antibodies profile. The 5- and 10-years survival rates of patients with anti-PM/Scl antibodies were 91% and 82% respectively, without differences with those without these antibodies (93% and 85%, respectively).

Conclusion: In Spanish SSc patients, the presence of anti-PM/Scl antibodies confer a distinctive clinical profile. However, anti-PM/Scl antibodies do not play a role in the prognosis of these patients.

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SAT0317

HDL-CHOLESTEROL EFFLUX CAPACITY IS DOWNREGULATED IN PATIENTS WITH SYSTEMIC SCLEROSIS.

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Background: It is well established that patients with systemic sclerosis (SS) show a disrupted lipid profile and an increased cardiovascular risk. Cholesterol efflux capacity (CEC) is the ability of high-density lipoprotein (HDL)-cholesterol to accept cholesterol from macrophages. CEC has been linked to cardiovascular events in the general population and to subclinical atherosclerosis in patients with rheumatoid arthritis and systemic lupus erythematosus.

Objectives: The main purpose of our study was to assess, for the first time, whether CEC is disrupted in patients with SS compared to controls. We also aimed to identify patients' characteristics that could explain such potential CEC disturbance.

Methods: Cross-sectional study that encompassed 188 individuals; 73 SS patients and 115 age- and sex-matched controls. CEC, using an *in vitro* assay, and lipoprotein serum concentrations were assessed in patients and controls. A multivariable analysis was performed to study the differences in CEC between patients and controls, and if SS-related data could explain CEC differences.

Results: CEC was downregulated in SS patients as compared to controls (beta coefficient -6 [95%CI -10 -2] %, $p=0.002$). This occurred independently of traditional cardiovascular risk factors, statin use or other variations in the lipid profile produced by the disease. Demographics and lipid profile were, in general, not related with CEC in both patients and controls. In this sense, only abdominal circumference showed a positive association with CEC in patients (beta coefficient 0.09 [95%CI 0.03-0.14], $p=0.002$) but not in controls. Similarly, no traditional

cardiovascular risk factors were related with CEC in both populations. Regarding lipid profile, no correlations were identified between the standard lipid profile molecules and CEC. Remarkably, the use of statins was not related to CEC in both patients and controls. Lastly, concerning SS related data, a negative association between mRSS and CEC was identified (beta coef. -1.08 [95%CI -2.03 -0.12] %, $p=0.028$).

Skin thickness through modified Rodnan (mRSS) was positively related to age and the presence of hypertension, but negatively associated with apolipoprotein B, apo B:A1 ratio, and CEC when univariate correlations were assessed (Table 4). When the relation of mRSS to these lipid-related molecules was adjusted for traditional CV risk factors, the statistical significance of mRSS with those molecules was maintained. Moreover, when the relation between mRSS and CEC was additionally adjusted for other lipid-related molecules, its significance was conserved (beta coef. -1.35 [95%CI -2.62 -0.08] %, $p=0.038$).

Conclusion: CEC is downregulated in SS patients independently of other inflammation-related lipid profile modifications that occur in the disease. Skin thickness is independent and inversely associated with CEC in SS patients.

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SAT0318

GENERALIZED INDICATOR OF RAYNAUD'S PHENOMENON EXPRESSION FOR EVALUATION OF CLINICAL EFFICACY OF PROSTANOID THERAPY

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Background: Raynaud's phenomenon (RP) secondary to rheumatic diseases (RD) can progress to irreversible tissue damage with digital ulceration, scarring and, rarely, gangrene requiring amputation¹. Current medical treatments for RP are far from ideal: they are often either ineffective and/or poorly tolerated, thus a significant proportion of patients discontinue drug therapy².

Objectives: To determine RP expression levels and to evaluate the long-term efficacy of iloprost and alprostadil in RP patients with RD.

Methods: Indicated therapy with intravenous iloprost (n=10), alprostadil (n=17) or their combinations (n=13) was carried out for three years in patients with secondary RP in RD. Frequency of Raynaud's attacks, digital ulcers (DU) formation and pain intensity on visual analogue scale (VAS) were evaluated. A control group included 30 patients with RP in RD who did not receive prostanoid therapy. By factor analysis method a generalized index of RP expression was identified, on the basis of which levels of RP expression were determined.

Results: "RP expression" scale, revealed as an indicator of RP generalized manifestation, was an average value of two subscales: (1) consisted of 4 indices "DU", "digital pitting scars", "phalange amputation" and "frequency of Raynaud's attack"; (2) included 3 indicators: "intensity of pain", "duration of illness", "whitening of fingers". Correlation of subscales showed their reliability ($r=0.294$, $p=0.053$). RP final expression (severity) was 1.51 ± 0.86 . A low level of RP expression had values below 0.65, a high level – over 2.37. At baseline, the high level of RP severity was defined in 16 (22.9%) patients, medium – in 43 (61.4%), low – in 11 (15.7%).

RP treatment with iloprost was effective in the healing of DU in 100% of patients and led to decrease of RP expression generalized index from 2.25 [1; 3] to 1.75 [1; 2] ($p=0.012$). Alprostadil therapy reduced pain intensity on VAS ($p<0.05$) and numbness during Raynaud's attacks ($p<0.01$) and decreased RP expression from 1 [1; 2] to 1 [0.5; 1.5] ($p=0.038$). Patients on prostanoids combination had new DU and amputations; pain intensity reduced by 47% ($p<0.05$), RP expression generalized indicator did not change.

Conclusion: Based on RP clinical manifestations in RD patients, a generalized index of RP expression was identified and levels of RP severity were determined. Treatment with iloprost or alprostadil has significant effects on reducing the clinical manifestations of RP with a corresponding decrease in its severity. Iloprost is indicated in patients with medium and high levels of RP expression index, alprostadil – with medium and low index and non-effectiveness of calcium channel blockers.