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Running header: Phase 2 seletalisib study in primary Sjögren's syndrome

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Abstract

Objectives

This phase 2 proof-of-concept study (NCT02610543) assessed efficacy, safety and effects on salivary gland inflammation of seletalisib, a potent and selective PI3Kδ inhibitor, in patients with moderate-to-severe primary Sjögren's syndrome (PSS).

Methods

Adults with PSS were randomised 1:1 to seletalisib 45 mg/day or placebo, in addition to current PSS therapy. Primary endpoints were safety and tolerability and change from baseline in ESSDAI score at Week 12. Secondary endpoints included change from baseline at Week 12 in ESSPRI score and histological features in salivary gland biopsies.

Results

Twenty-seven patients were randomised (seletalisib *n*=13, placebo *n*=14); 20 completed the study. Enrolment challenges led to early study termination with loss of statistical power (36% vs 80% planned). Nonetheless, a trend for improvement in ESSDAI and ESSPRI (difference vs placebo: –2.59 [95% CI –7.30, 2.11; *P*=0.266] and –1.55 [95% CI –3.39, 0.28], respectively) was observed at Week 12. No significant changes were seen in saliva and tear flow. Serious adverse events (AEs) were reported in 3/13 of patients receiving seletalisib versus 1/14 for placebo and 5/13 versus 1/14 discontinued due to AEs, respectively. Serum IgM and IgG concentrations decreased in the seletalisib group versus placebo. Seletalisib demonstrated efficacy in reducing size and organisation of salivary gland inflammatory foci and in target engagement, thus reducing PI3K-mTOR signalling compared with placebo.

Conclusion

Despite enrolment challenges, seletalisib demonstrated a trend towards clinical improvement in patients with PSS. Histological analyses demonstrated encouraging effects of seletalisib on salivary gland inflammation and organization.

Trial registration number: NCT02610543

Keywords

Phosphatidylinositol 3-kinase delta (PI3Kδ); primary Sjögren's syndrome; seletalisib; proof-of-concept; histology

Key messages

- Seletalisib demonstrated a trend towards clinical improvement in patients with PSS despite enrolment-related underpowering
- Histological analyses demonstrated encouraging effects of seletalisib on salivary gland inflammation and organization
- Seletalisib or other PI3Kδ inhibitors could be new effective drugs in PSS requiring future development

Introduction

Primary Sjögren's syndrome (PSS) is a chronic, inflammatory, autoimmune disease characterised by focal lymphocytic infiltration and progressive functional impairment of the exocrine glands, often associated with systemic symptoms, B-cell hyperactivation, autoantibody formation, and increased risk of lymphoma development (1-3).

Pathway-specific biologics have been investigated in PSS with diverse results (2, 4). Two controlled trials of rituximab (5, 6) and two studies of abatacept (7, 8) did not meet their primary endpoints. Conversely, a small study with a CD40-targeted antibody, CFZ533, reported significant amelioration of European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI), and a trend towards improvement in EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) (9).

Expression of phosphatidylinositol 3-kinase delta (PI3Kδ) is greatly enriched in leukocytes (10). PI3Kδ signalling mediates many aspects of B cell homeostasis and regulates B cell receptor signal transduction (11, 12). Blockade of PI3Kδ is under evaluation in B cell malignancies and autoimmune conditions characterized by aberrant B cell activation (13-16).

Following receptor activation, PI3Kδ elicits downstream signals though the AKT-mTOR pathway (12), resulting in phosphorylation of molecules including ribosomal protein S6 (pS6) (17, 18). In patients with PSS, we recently demonstrated that the PI3Kδ pathway is active in infiltrated salivary glands, and that the amount of PI3Kδ mRNA transcript expression and downstream pS6 phosphorylation correlates with B cell hyperactivity (3).

Seletalisib is a potent and selective oral PI3Kδ inhibitor (17, 19). In a mouse model of PSS, treatment with seletalisib blocked PI3Kδ activity, demonstrated by significant reduction of pS6 phosphorylation and decreased accumulation of B and T lymphocytes and plasma cells. Treatment with seletalisib also reduced autoantibody titres and improved saliva production (3), providing a strong rationale for the evaluation of seletalisib in patients with PSS.

Here we report the results of a phase 2 proof-of-concept study (NCT02610543; clinicaltrials.gov) assessing the efficacy, pharmacokinetics (PK), safety and tolerability of seletalisib in patients with moderate-to-severe PSS. Despite early termination and underpowering due to recruitment challenges, there was a trend for

improvement in ESSDAI and ESSPRI with seletalisib as well as encouraging histological changes in both the size and organization of salivary gland infiltrates.

Methods

Study design

A phase 2 randomised, double-blind, placebo-controlled, proof-of-concept study (NCT02610543) conducted between 28 October 2015 and 5 December 2017 across 16 sites in France, Italy, Spain, Sweden, and the UK. Patients were randomised 1:1 to oral seletalisib 45 mg once daily or matching placebo, in addition to current PSS therapy, according to a predetermined randomisation schedule (supplementary materials, section Methods). The study comprised a 12-week treatment period and a 4-week safety follow-up.

Patients

Eligible patients were aged 18–75 years with moderate-to-severe PSS meeting the American-European Consensus Group criteria (20), total ESSDAI score ≥5, and positive for anti-Sjögren's-syndrome-related antigen A (SSA; Ro) and/or anti-Sjögren's-syndrome-related antigen B (SSB; La) autoantibodies. Eligibility required an unstimulated salivary flow rate of >0 mL/15 min and a salivary gland biopsy in the prior 12 months, or during screening. Repeat biopsy was also requested at Week 12. Additional inclusion and exclusion criteria are provided in Supplementary Table S1.

The study was conducted in accordance with the Declaration of Helsinki and the protocol approved by national or regional independent ethics committees. Written informed consent was obtained from all patients before enrolment.

Endpoints

The primary objectives were safety and tolerability and systemic disease activity. The primary efficacy endpoint was change from baseline in ESSDAI score at Week 12.

Secondary endpoints were changes from baseline in ESSDAI score at Weeks 4 and 8; changes from baseline in ESSPRI, saliva production, tear production (Schirmer’s I test), and pre- and post-dose seletalisib plasma concentrations at Weeks 4, 8, and 12.

Exploratory efficacy endpoints included changes in salivary gland biopsies at Week 12 and those listed in the supplementary materials, section Methods.

Safety and tolerability assessments included incidence of adverse events, changes in clinical laboratory measurements, vital signs, and 12-lead electrocardiograms (ECGs).

Histology

Minor salivary gland biopsies from screening and Week 12 were fixed, sectioned, and stained with haematoxylin and eosin (H&E), CD3/CD20 (Agilent Dako, Stockport, UK), and CD21 (Agilent Dako). Staining was detected by immunohistochemistry using the Leica Bond RX automated staining system (Leica Biosystems, Milton Keynes, UK) (21). Analysis of histological features was conducted in paired biopsies on sections obtained from two cutting levels taken 100 µm apart using Leica Slidepath software (version 4.0.7) as detailed in supplementary materials, section Methods.

Manual immunofluorescence staining for CD20, CD138, CD3 and pS6 was performed as previously described (3) on sequential sections. Evaluation of total CD20 (B cells), $pS6^+$ CD20, CD138 (plasma cells), $pS6^+$ CD138, CD3 (T cells), and $pS6^+$ CD3 cell numbers was performed using Definiens TissueStudio® (Definiens AG, Munich, Germany; supplementary materials, section Methods).

Statistical analysis

Recruitment of 58 patients was originally planned to detect a difference of 3.8 points in mean change from baseline in ESSDAI between seletalisib and placebo at Week 12 with 80% power, at a two-sided significance level of 0.05.

Safety analyses were based on the safety set, which comprised all randomised patients who received at least one dose of study drug. Efficacy analyses were based on the full analysis set, which comprised all patients in the safety set who had at least one post-baseline efficacy assessment.

The primary efficacy endpoint, change from baseline in ESSDAI at Week 12, was analysed by a mixed model for repeated measures (MMRM) to account for missing data, with covariates of treatment, visit, baseline ESSDAI score, and treatment by visit interaction. Least squares (LS) means were calculated for change from baseline at Week 12 for each group, and differences between treatments with 95% confidence intervals (CIs) and p values were reported. Observed ESSDAI data were also analysed by analysis of covariance (ANCOVA) with no imputation of missing data. The minimal clinically important improvement in ESSDAI score was defined as a decrease of three points. A post-hoc Bayesian analysis was conducted to interpret the results based on the limited observed data (supplementary materials, section Methods).

For analysis of secondary and exploratory endpoints see the supplementary materials, section Methods.

Results

Patient disposition and demographics

Fifty-one patients were screened, 27 patients randomised (seletalisib *n*=13, placebo *n*=14), and 20 completed the study (Fig. 1). Due to enrolment challenges, the study was terminated early; nearly 2 years was needed to recruit the 51 patients. Some of the issues identified affecting recruitment were competition with several other studies; requirement for salivary gland biopsies; or number of study visits. Moreover, due to safety concerns related to potential interaction, the number of concomitant medications allowed during the study were limited, further restricting the inclusion criteria. Compared with the power of the original study design (80%), the smaller than planned population (*n*=27 vs *n*=58, respectively) resulted in the study being statistically underpowered (36%).

Mean (SD) age of the randomised patients was 56.4 (13.6) years; the majority were female (92.6%) and white (96.3%), with a median (range) duration since diagnosis of 6.1 (0–26) years (table 1). Baseline characteristics were generally well balanced between the two groups.

Efficacy

Both groups showed an improvement in ESSDAI score in the primary analysis using MMRM; the LS mean (SE) change from baseline to Week 12 was greater in the seletalisib group (–5.4 [1.7]) vs placebo (–2.8 [1.5]). The treatment difference versus placebo was –2.59 (95% CI –7.30, 2.11), which was not statistically significant (*P*=0.266; Fig. 2A). Results using ANCOVA with observed case analysis supported the primary analysis; LS mean difference versus placebo was –2.93 (95% CI: –8.35, 2.50).

A higher percentage of patients in the seletalisib group achieved the minimal clinically important improvement in ESSDAI score (greater than 3-point reduction) compared with the placebo group at Week 4: 7/13 (53.8%) vs 3/14 (21.4%); at Week 8: 8/10 (80.0%) vs 4/13 (30.8%); and at Week 12: 6/9 (66.7%) vs 6/11 (54.5%), respectively (Fig. 2B). Using an intent-to-treat analysis, results for the seletalisib group vs the placebo group were at Week 4: 7/13 (53.8%) vs 3/14 (21.4%); at Week 8: 8/13 (61.5%) vs 4/14 (28.6%); and at Week 12 6/13 (46.2%) vs 6/14 (42.9%). Changes in the individual ESSDAI domain scores are shown in Supplementary Table S2.

A post-hoc Bayesian analysis to determine the probability of a true difference in ESSDAI score between the groups based on the limited observed data demonstrated a mean change from baseline similar to the primary efficacy analysis (seletalisib –5.9 vs placebo –3.0). Furthermore, the treatment difference versus placebo was also comparable to the primary efficacy analysis: –2.9 (95% credible intervals: –2.5, 8.3). The analysis suggested that the probability of a true difference versus placebo of >3 points (minimal clinically important improvement), and >3.8 points (treatment difference used for the original sample size calculation) was 48.8% and 36.8%, respectively.

Change from baseline in ESSPRI score was also greater in the seletalisib group versus placebo at all time points to Week 12 (Fig. 2C). The LS mean difference versus placebo was –1.55 (95% CI –3.39, 0.28). For the individual domains of ESSPRI, LS mean difference versus placebo was statistically significant for fatigue (–2.48 [95% CI: –4.22, –0.75]) but improvements were not statistically significant for the other domains (dryness –0.92 [95% CI: –3.47, 1.63], and limb pain –1.22 [95% CI: –3.80, 1.36]).

No significant changes in saliva or tear production were observed between the seletalisib and placebo groups. Change from baseline to Week 12 for LS mean difference versus placebo in stimulated salivary flow rate was 0.02 (95% CI –0.27, 0.31) mL/min (Supplementary Fig. S1A), in unstimulated salivary flow rate was –0.02 (95% CI –0.10, 0.06) mL/min (Supplementary Fig. S1B), and in Schirmer's I test sum score was –1.41 (95% CI –10.35, 7.52).

Serum concentrations of IgG and IgM decreased with seletalisib versus placebo at Week 12, although IgA remained stable (Supplementary Figs. S2A–S2C). Change from baseline to Week 12 for LS mean difference versus placebo in IgG was –3.53 (95% CI: –5.55, –1.51) g/L, in IgM was –0.40 (95% CI: –0.68, –0.12) g/L, and in IgA was –0.03 (95% CI: –0.04, 0.34) g/L.

Improvement versus placebo was seen for change from baseline in fatigue visual analogue scale (VAS; Supplementary Fig. S3), overall dryness VAS, oral dryness VAS, dyspareunia VAS, pain VAS, and PROFAD-SSI, but not for change from baseline in tear film break-up time (TBUT), ocular dryness VAS, vaginal dryness VAS, Physician's Global Assessment of Disease Activity (PhGADA), anti-SSA and anti-SSB status, and complement C3 and C4 concentrations (Supplementary Table S3).

Safety and tolerability

Almost all patients reported adverse events (AEs) and 10/13 (76.9%) patients in the seletalisib group and 3/14 (21.4%) in the placebo group had drug-related AEs (table 2). The most common AE was diarrhoea, reported by 5/13 (38.5%) in the seletalisib group and none in the placebo group. Of these, 3/13 (23.1%) seletalisib-treated patients had AEs of diarrhoea that were considered drug-related. In the seletalisib group, 5/13 (38.5%) discontinued due to AEs (diarrhoea [*n*=1], increased hepatic enzyme [*n*=1], angioedema, and urticaria [*n*=1], allergic dermatitis [*n*=1] and erythema multiforme [*n*=1]), and 1/14 (7.1%) in the placebo group (increased blood creatinine phosphokinase and renal impairment). Three patients reported serious AEs (SAEs) in the seletalisib group: one patient presented with shoulder monoarthritis with associated calcium pyrophosphate crystals; one reported severe diarrhoea; and one presented with angioedema and urticaria. In the placebo group, one patient reported a SAE of inflammatory myopathy. There were no deaths during the study.

There were no clinically relevant differences between groups in haematology, serum chemistry, urinalysis, vital signs, and ECG. One patient in the seletalisib group had markedly abnormal ALT values ≥5.0 times the upper limit of normal (ULN), and AST ≥3.0 times the ULN at Week 6, which led to discontinuation.

Pharmacokinetics

Plasma concentrations of seletalisib increased over the treatment period. In the seletalisib group, geometric mean pre-dose concentrations increased from 25.1 ng/mL at Week 1 to 820.0 ng/mL at Week 4, and then remained stable for Week 8 (778.0 ng/mL), and Week 12 (969.8 ng/mL).

Histology

Salivary gland biopsies were obtained from consenting patients at baseline (seletalisib *n*=13, placebo *n*=13), and Week 12 (seletalisib *n*=7, placebo *n*=11). Lymphocytic foci, B and T cell segregation, and germinal centres were identified with H&E, CD3/CD20 and CD21 staining, respectively (Fig. 3A, Supplementary Fig. S4). At baseline, minor salivary gland biopsies showed broadly similar features between groups although percentage infiltration and focus score were slightly higher in the placebo group. At Week 12, biopsies from the seletalisib group showed a reduction from baseline in size, overall percentage of infiltration, and cellular organization of

mononuclear inflammatory cell foci compared with placebo (Fig. 3). Of seletalisib-treated patients with histological data at Week 12, 6/7 were ESSDAI responders (greater than 3-point reduction in ESSDAI score), and also had decreases in infiltration, foci with follicular dendritic cells, segregation, and germinal centres. Of the placebo-treated patients, 5/11 were ESSDAI responders; not all responders had concomitant reductions in organization of foci.

The number of infiltrating immune cells was quantified using Definiens TissueStudio® image analysis; a decrease was observed in B lymphocytes, T lymphocytes, and plasma cells within the lymphocytic infiltrates (Fig. 4). Interestingly, an increase in B cells outside the foci was also observed, suggesting foci disaggregation (Supplementary Fig. S5), which was consistent with the observed decrease in focus score, and average foci area in biopsies from the seletalisib group. PS6 staining decreased in the seletalisib group versus placebo in B cells, but not in T cells or plasma cells (Supplementary Fig. S6).

Discussion

Despite increased understanding of disease pathogenesis and management, PSS still represents an unmet clinical need. Large clinical trials with biologics have so far failed to confirm proof of concept in this disease and the need for treatment in systemically active patients is still pressing. Here we report the results of a phase 2 proof-of-concept study using seletalisib, a PI3Kδ-specific inhibitor, in patients with moderate-to-severe PSS.

While the study failed to meet its primary endpoint owing to premature termination due to enrolment challenges, data analysis demonstrated a trend towards clinical improvement in ESSDAI total score. Moderate improvements were also detected in ESSPRI, together with improvements in the glandular, articular, and biological ESSDAI domain scores, and decreases in IgG and IgM concentrations. Moreover, histological analysis of salivary gland biopsies demonstrated encouraging effects of seletalisib on the organization and extent of lymphocytic infiltration in salivary gland biopsies obtained at Week 12.

Recruitment for this study was challenging and premature termination resulted in the actual power being 36% versus the planned power of 80%. The smaller than planned number of patients is likely to have affected the significance of ESSDAI improvements. While a prominent difference in ESSDAI scores between seletalisib- and placebo-treated patients (80.0% and 30.8%, respectively) was observed at Week 8, the difference was reduced at Week 12. This reduction may be related to missing data, where two patients receiving placebo trending toward worsening and one patient receiving seletalisib trending toward improvement had missing Week 12 ESSDAI scores. We chose not to impute for missing values as we felt this analysis would not be robust given the small number of patients and visits. A post-hoc Bayesian analysis of the observed data for the primary efficacy endpoint suggested that, if the planned sample size had been achieved, the study may have demonstrated a statistically significant effect of seletalisib treatment versus placebo.

Modest improvements were detected in total ESSPRI and in the fatigue domain, while improvements in dryness and limb pain domain scores, as well as in overall and oral dryness VAS were not statistically significant. Interestingly, and consistent with observations in an animal model of PSS (3), a modest increase from baseline in stimulated salivary flow was demonstrated in seletalisib-treated patients at Weeks 4 and 8. At Week 12, however, change from baseline was similar to that in the placebo

group. Unstimulated salivary flow did not improve in this study compared with placebo.

More consistent results were observed in biological outcome measures of immunoglobulin levels and histology. We observed a reduction in immunoglobulins, in particular in IgM, consistent with results of another PI3Kδ inhibitor, leniolisib, in a small first-in-human study of patients with activated PI3Kδ syndrome, a rare immunodeficiency resulting from gain-of-function mutations in genes for PI3Kδ (22). We also observed significant changes in salivary gland pathology: salivary gland infiltrates from seletalisib-treated patients showed decreases in both the organization and extent of lymphocytic infiltration. These observations were consistent with data obtained in a murine model recapitulating features of PSS (focal sialoadenitis), in which seletalisib decreased accumulation of lymphocytes in the salivary glands, as well as focus score, average focus area, and degree of aggregate segregation compared with controls (3). However, only a small number of paired biopsy samples were available, and it was therefore not appropriate to calculate p values. Automatic quantification of the inflammatory infiltrates also confirmed the decrease from baseline in lymphocyte numbers and PI3Kδ engagement, as demonstrated by the decrease in $pS6^+$ cell numbers. Interestingly, B cells appeared to be more susceptible to PI3Kδ inhibition as decreases in $pS6^+$ T and plasma cells were not observed. Histological analysis also demonstrated different effects in the foci compared with the sparse population of immune cells in the glands. This suggests that PI3Kδ inhibition affects cell aggregation in the salivary glands, compromising the process of T/B cell activation, as reflected in the observed decrease in immunoglobulins. In line with the results in this study, leniolisib, another PI3Kδ inhibitor, also showed a modest improvement in biological endpoints but did not achieve significant clinical results in patients with PSS (23).

The most common AE in the seletalisib group was diarrhoea, previously described as a common adverse event in patients receiving the PI3Kδ inhibitor idelalisib for chronic lymphocytic leukaemia and follicular lymphoma (24). A pathogenic association with regulatory T cell function could be responsible for this side effect (25, 26). In our study, the gastrointestinal side effects were of moderate severity in most patients but one patient experienced severe diarrhoea; in one patient, moderately severe diarrhoea led to discontinuation from the study. This, together with the number of discontinuations seen in the seletalisib group, suggests that a lower seletalisib dose or a more selective PI3K inhibitor may be better tolerated in this patient population.

In summary, while not meeting all efficacy endpoints due to enrolment challenges, this study supports targeting the PI3K pathway as a novel therapeutic approach in PSS. The trends towards improvement observed in this study and the post-hoc Bayesian analysis suggest the probability of a true difference between seletalisib and placebo. Moreover, reductions in immunoglobulins and pathological improvements revealed by histological analysis demonstrated PI3Kδ blockade at the biological level in seletalisib-treated patients. There were, however, no significant effects on saliva or tear production. SAEs were uncommon but gastrointestinal side effects were an issue. Larger studies with specific PI3Kδ inhibitors and potentially with patient stratification could be considered in the future.

Table 1 Patient demographics and baseline characteristics

Characteristic	**Seletalisib (*n*=13)**	**Placebo (*n*=14)**	**All patients (*N*=27)**
Age, mean (SD)	52.2 (16.1)	60.2 (9.9)	56.4 (13.6)
Gender, female, *n* (%)	12 (92.3)	13 (92.9)	25 (92.6)
Ethnicity, *n* (%)			
White	13 (100)	13 (92.9)	26 (96.3)
Duration of PSS*, median (range), years	6.1 (0–20)	7.6 (0–26)	6.1 (0–26)
ESSDAI score#, mean (SD)	10.6 (4.3)	13.1 (8.6)	11.9 (6.8)
High disease activity (ESSDAI >13), *n* (%)	4 (30.8)	5 (35.7)	9 (33.3)
Moderate disease activity (ESSDAI ≥5 to ≤13), *n* (%)	9 (69.2)	9 (64.3)	18 (66.7)
ESSPRI score, mean (SD)	5.5 (2.1)	6.4 (1.7)	6.0 (1.9)
Salivary flow (mL/min), mean (SD)			
Unstimulated	0.1 (0.1)	0.1 (0.2)	0.1 (0.1)
Stimulated	0.6 (0.5)	0.7 (0.8)	0.6 (0.7)
Schirmer's I test (mm), mean (SD)	12.0 (18.7)	9.3 (11.7)	10.6 (15.2)
Immunoglobulins at baseline (g/L), mean (SD)			
IgG	15.7 (5.1)	17.2 (6.9)	16.5 (6.0)
IgM	2.3 (3.8)	1.7 (1.8)	2.0 (2.9)
IgA	3.2 (0.8)	3.0 (1.3)	3.1 (1.1)
Complement at baseline (g/L), mean (SD)			
C3	1.2 (0.2)	1.2 (0.3)	1.2 (0.3)
C4	0.3 (0.1)	0.2 (0.1)	0.2 (0.1)
Autoantibody positive at baseline, *n* (%)			
Anti-SSA/Ro52	12 (92.3)	11 (78.6)	23 (85.2)
Anti-SSA/Ro60	13 (100.0)	14 (100.0)	27 (100.0)
Anti-SSB	6 (46.2)	9 (64.3)	15 (55.6)
Baseline treatments, *n* (%)			
Cholinergics	4 (30.8)	3 (21.4)	7 (25.9)
Anti-malarials	5 (38.5)	3 (21.4)	8 (29.6)

Prednisone	2 (15.4)	1 (7.1)	3 (11.1)
Immunosuppressants	0	1 (7.1)	1 (3.7)

[a]Median duration since diagnosis and [b]mean ESSDAI scores were slightly lower in the seletalisib group compared with the placebo group, however, statistical differences were not measured between groups for baseline demographics.

ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; Ig, immunoglobulin; SD, standard deviation; SSA, Sjögren's-syndrome-related antigen A; SSB, Sjögren's-syndrome-related antigen B.

Table 2 Incidence of adverse events[a] (safety set)

***n* (%)**	**Seletalisib (*n*=13)**	**Placebo (*n*=14)**
Any AE	13 (100)	13 (92.9)
Drug-related AEs[b]	10 (76.9)	3 (21.4)
Discontinuations due to AEs	5 (38.5)[c]	1 (7.1)[d]
Serious AEs	3 (23.1)	1 (7.1)
Deaths	0	0
Incidence of AEs reported in ≥2 patients overall		
Diarrhoea	5 (38.5)	0
Headache	3 (23.1)	2 (14.3)
Abdominal pain	2 (15.4)	0
Back pain	2 (15.4)	0
Nausea	2 (15.4)	1 (7.1)
Neck pain	2 (15.4)	0
Rash	2 (15.4)	0
Arthralgia	1 (7.7)	1 (7.1)
Constipation	1 (7.7)	1 (7.1)
Fatigue	1 (7.7)	2 (14.3)
Gingivitis	0	2 (14.3)
Hypertension	0	2 (14.3)
Myalgia	1 (7.7)	1 (7.1)
Respiratory tract infection	1 (7.7)	1 (7.1)
Urinary tract infection	1 (7.7)	1 (7.1)
Incidence of drug-related AEs[b] reported in ≥1 patient overall		
Diarrhoea	3 (23.1)	0
Alanine aminotransferase increased	1 (7.7)	0
Angioedema	1 (7.7)	0
Aspartate aminotransferase increased	1 (7.7)	0
Blood alkaline phosphatase increased	1 (7.7)	0
Conjunctivitis	1 (7.7)	0
Dermatitis allergic	1 (7.7)	0
Dysgeusia	1 (7.7)	0

Erythema multiforme	1 (7.7)	0
Flushing	1 (7.7)	0
Hepatic enzyme increased	1 (7.7)	0
Herpes zoster	1 (7.7)	0
Nausea	1 (7.7)	0
Neutrophil count decreased	1 (7.7)	0
Rash	1 (7.7)	0
Respiratory tract infection	1 (7.7)	0
Tracheitis	1 (7.7)	0
Urticaria	1 (7.7)	0
Vertigo	1 (7.7)	0
White blood cell count decreased	1 (7.7)	0
Constipation	0	1 (7.1)
Gingivitis	0	1 (7.1)
Headache	0	1 (7.1)
Hypertension	0	1 (7.1)
Oral pain	0	1 (7.1)
Rash maculo-papular	0	1 (7.1)
Rash vesicular	0	1 (7.1)
Sensory disturbance	0	1 (7.1)

[a] All AEs were treatment-emergent occuring during the study following at least 1 dose of study drug

[b] Designated as related to study drug by the investigator.

[c] Discontinuations due to AEs were diarrhoea (1 patient), increased hepatic enzyme (1 patient), angioedema and urticaria (1 patient), allergic dermatitis (1 patient) and erythema multiforme (1 patient).

[d] Discontinuations due to AEs were increased blood creatinine phosphokinase and renal impairment (1 patient).

AE, adverse event.

Figure legends

Fig. 1. Patient disposition.
AE, adverse event.

Fig. 2. ESSDAI and ESSPRI scores up to Week 12.
(A) Change from baseline in ESSDAI score; (B) Percentage of patients with a ≥3 point reduction from baseline in ESSDAI score; (C) Change from baseline in ESSPRI score (full analysis set). Change from baseline to Week 12 in ESSDAI (and ESSPRI) were analysed by MMRM with treatment, visit, and treatment by visit interaction as factors and baseline ESSDAI (ESSPRI) score as a covariate. The minimal clinically important improvement in ESSDAI score was defined as a decrease of at least 3 points.
ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; LS, least squares; MMRM, mixed model for repeated measures; SE, standard error.
In line graphs, seletalisib and placebo results have been offset for clarity.

Fig. 3. Histological results from paired minor salivary gland biopsies.
(A) Representative sections from placebo-treated and seletalisib-treated patients at screening/baseline and Week 12. In H&E stained sections, lymphocytic foci are indicated with arrows; margins of the foci are marked with green lines. In CD3/CD20 stained sections, T cells are indicated by brown staining, B cells are indicated by red staining and foci are indicated with arrows. Germinal centres are indicated with arrows where CD21 staining (brown) overlapping with lymphocytic foci identified by H&E staining. Change from baseline to Week 12 in histological parameters: (B) average focus area (mean of area within the margin of individual lymphocytic foci); (C) focus score (the number of lymphocytic foci per 4 mm^2 salivary gland tissue); (D) percentage infiltration; (E) percentage of foci with follicular dendritic cells; (F) percentage of germinal centres; (G) percentage of T- and B-cell segregation.
H&E, haematoxylin and eosin.
Individual patient data from paired biopsies (at baseline and Week 12) are shown for each group.

Fig. 4. Absolute cell count analysis of infiltrating cells in paired minor salivary gland biopsies.

Change from baseline to Week 12 in (A) B ($CD20^+$) lymphocyte, T ($CD3^+$) lymphocyte, and ($CD138^+$) plasma cell count within lymphocytic aggregates; (B) B ($CD20^+$) lymphocyte, T ($CD3^+$) lymphocyte, and ($CD138^+$) plasma cell count within non-aggregated glandular area; (C) proportion of $pS6^+$ B ($CD20^+$) lymphocyte, $pS6^+$ T ($CD3^+$) lymphocyte, and $pS6^+$ ($CD138^+$) plasma cell count within lymphocytic aggregates. Individual patient data from paired biopsies (at baseline and Week 12) are shown for each group.

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Data sharing statement

Due to the small sample size in this trial, Individual Patient Data cannot be adequately anonymised and there is a reasonable likelihood that individual participants could be re-identified. For this reason, data from this trial cannot be shared.

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