NOVARTIS

Global Clinical Development - General Medicine

VAY736

Clinical Trial Protocol CVAY736A2201

A randomized, double-blind, placebo-controlled multicenter phase 2 dose-ranging study to assess the safety and efficacy of multiple ianalumab doses administered subcutaneously in patients with moderate to severe primary Sjögren's Syndrome

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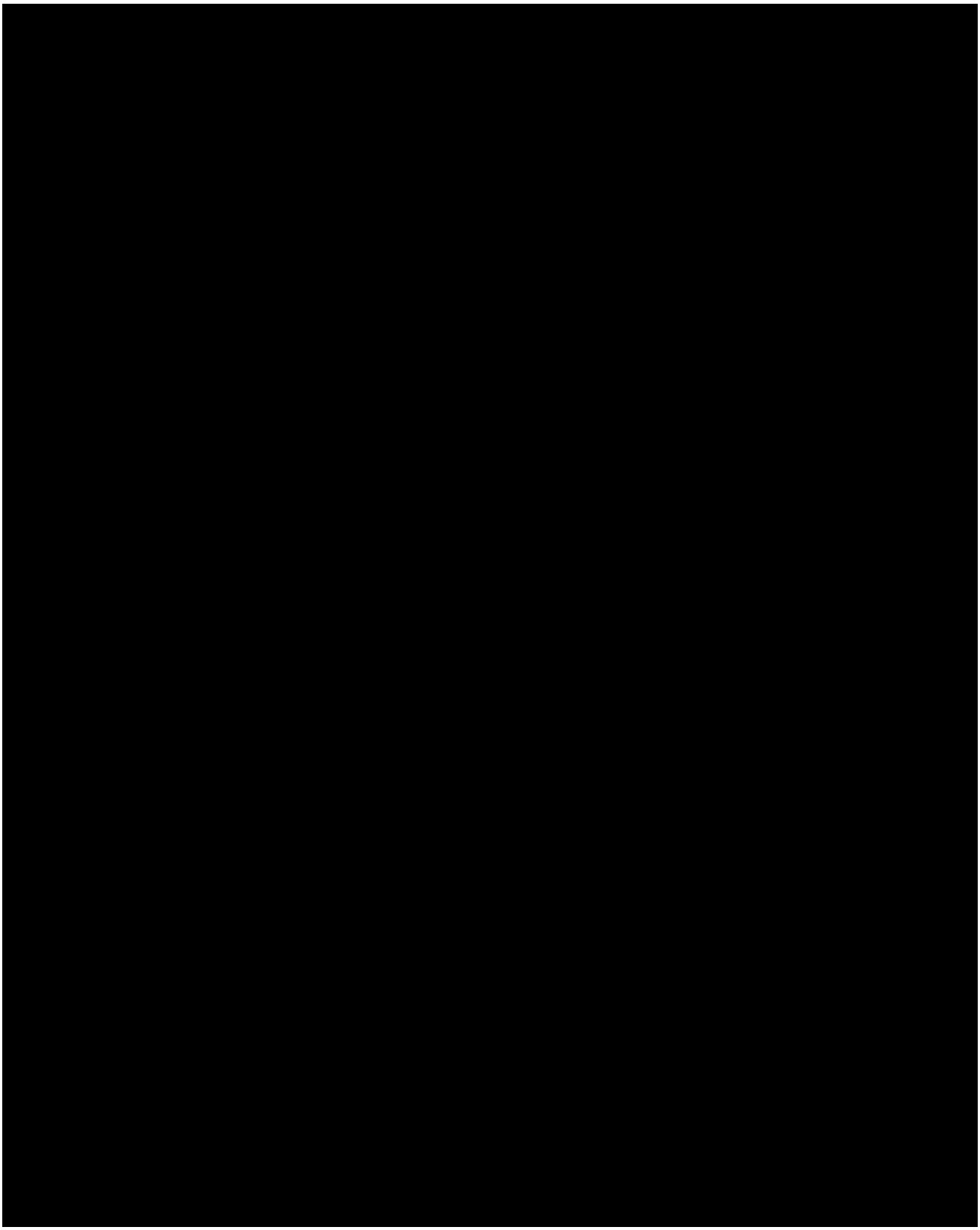
List of abbreviations

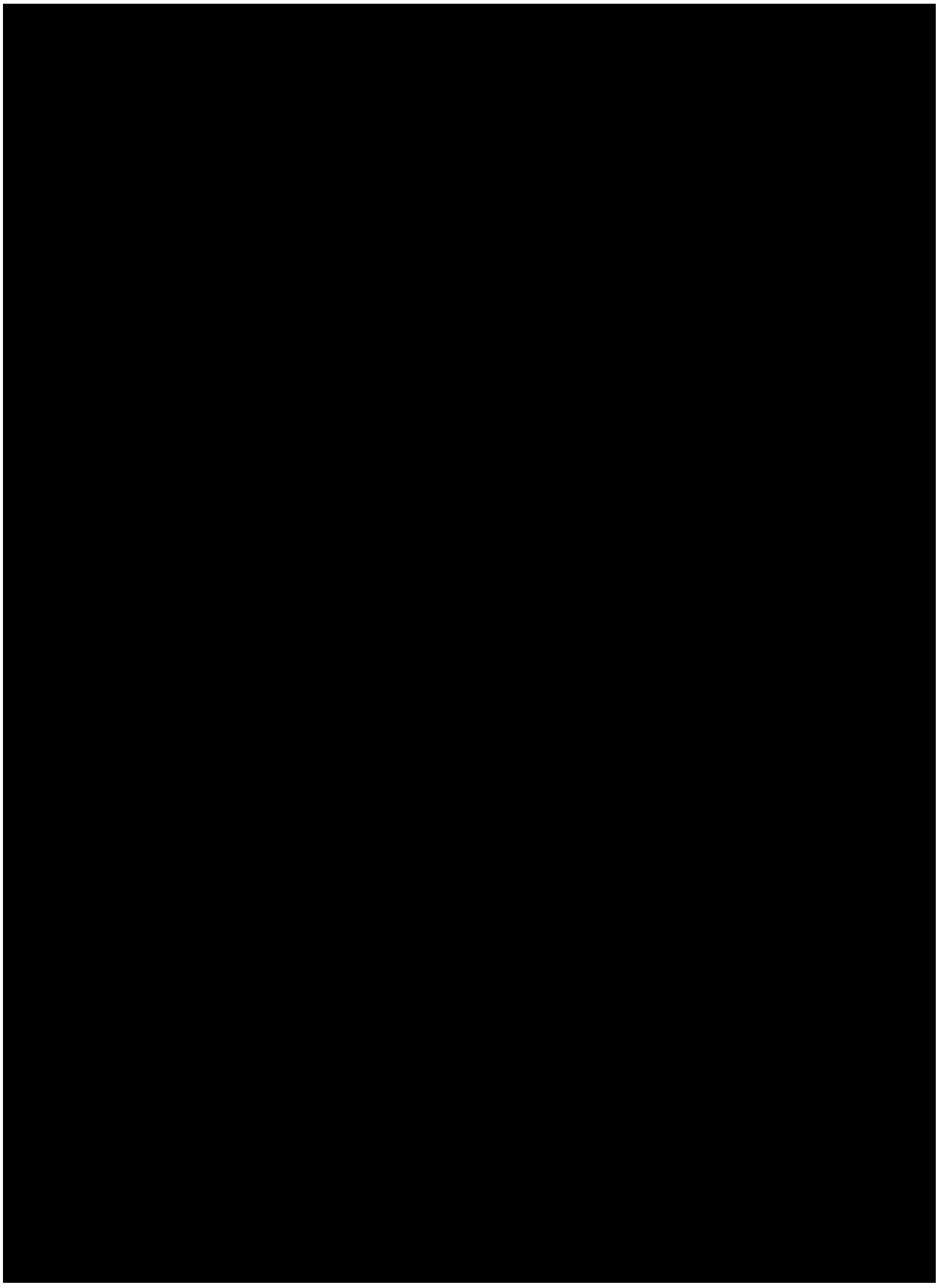
ADA	Anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
AE	Adverse Event
AECG	American European Consensus Group
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BAFF	B-cell activating factor
CFR	US Code of Federal Regulations
CLL	Chronic lymphocytic leukemia
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
[redacted]	[redacted]
CTC	Common Terminology Criteria
CTRD	Clinical Trial Results Database
DMARD	Disease modifying anti rheumatic drug
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
EoS	End of Study
EOT	End of Treatment
[redacted]	[redacted]
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
GCP	Good Clinical Practice
IA	Interim analysis
IC	Informed consent
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immunogenicity
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
IWRS	Interactive web response system
LFT	Liver function test
LON	Late onset neutropenia
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed-effect model repeat measurement
NSAID	Non-steroidal anti-inflammatory drug
OC/RDC	Oracle Clinical Remote Data Capture

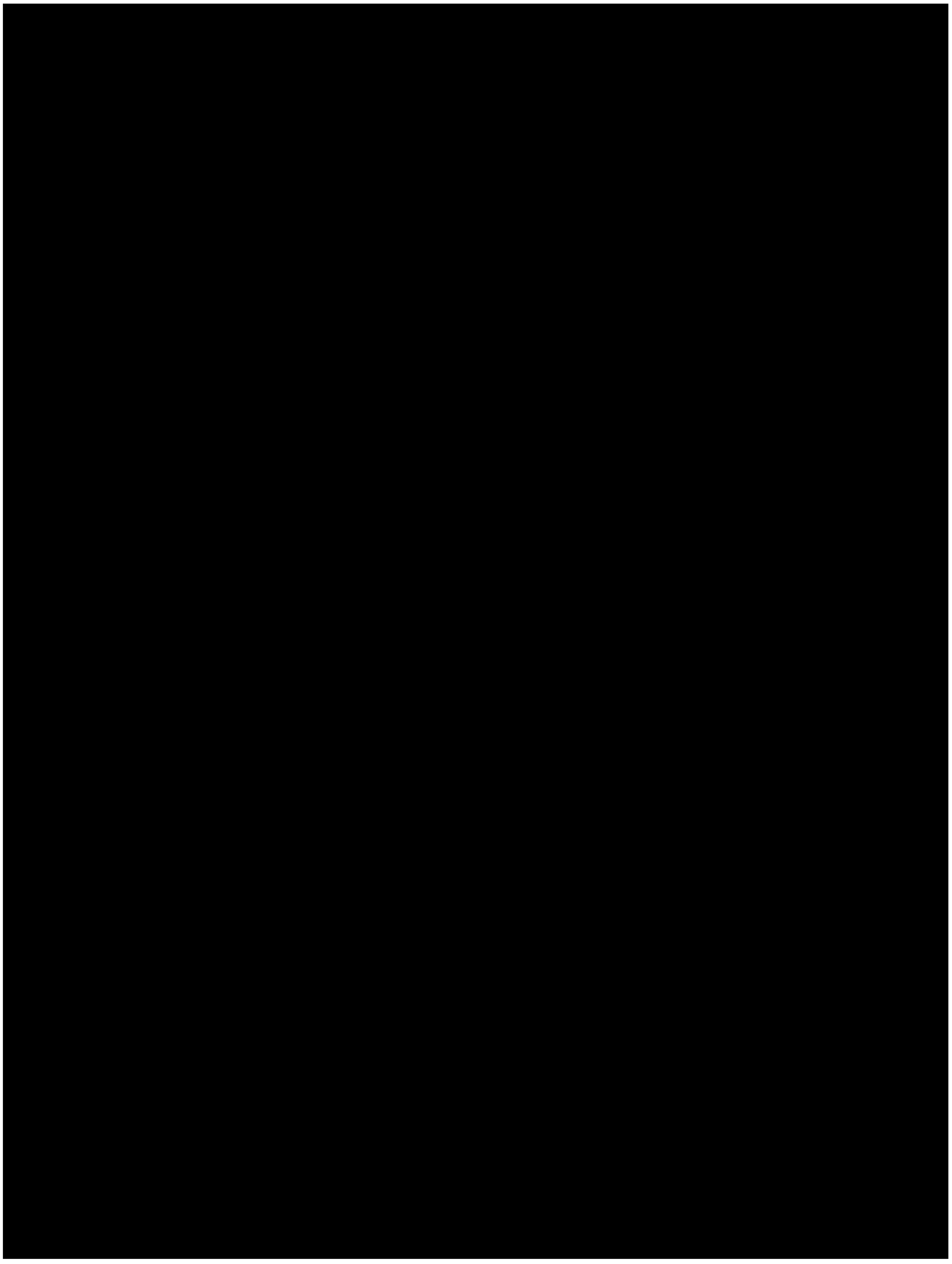
PaGA	Patient's global assessment
PhGA	Physician's global assessment
PoC	Proof of Concept
PRO	Patient reported outcome
pSS	Primary Sjögren's Syndrome
PT	Preferred Term
q4w	Every four weeks
RA	Rheumatoid Arthritis
RO	Receptor Occupancy
s.c.	subcutaneous
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SLE	Systemic Lupus Erythematosus
SoC	Standard of Care
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Study Treatment Discontinuation
WHO	World Health Organization
WoC	Withdrawal of Consent
WOCBP	Women of child-bearing potential
[redacted]	[redacted]

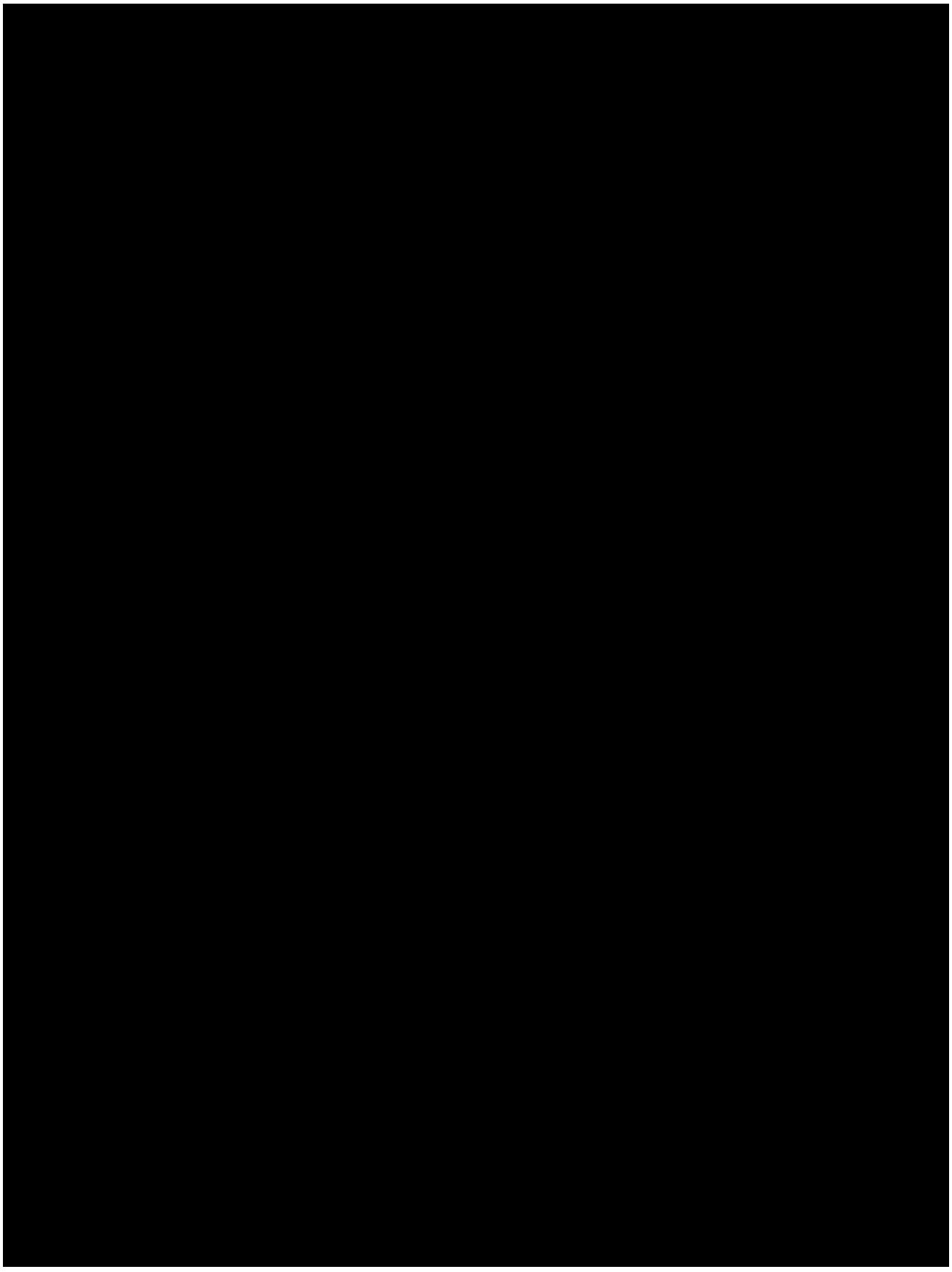
Glossary of terms

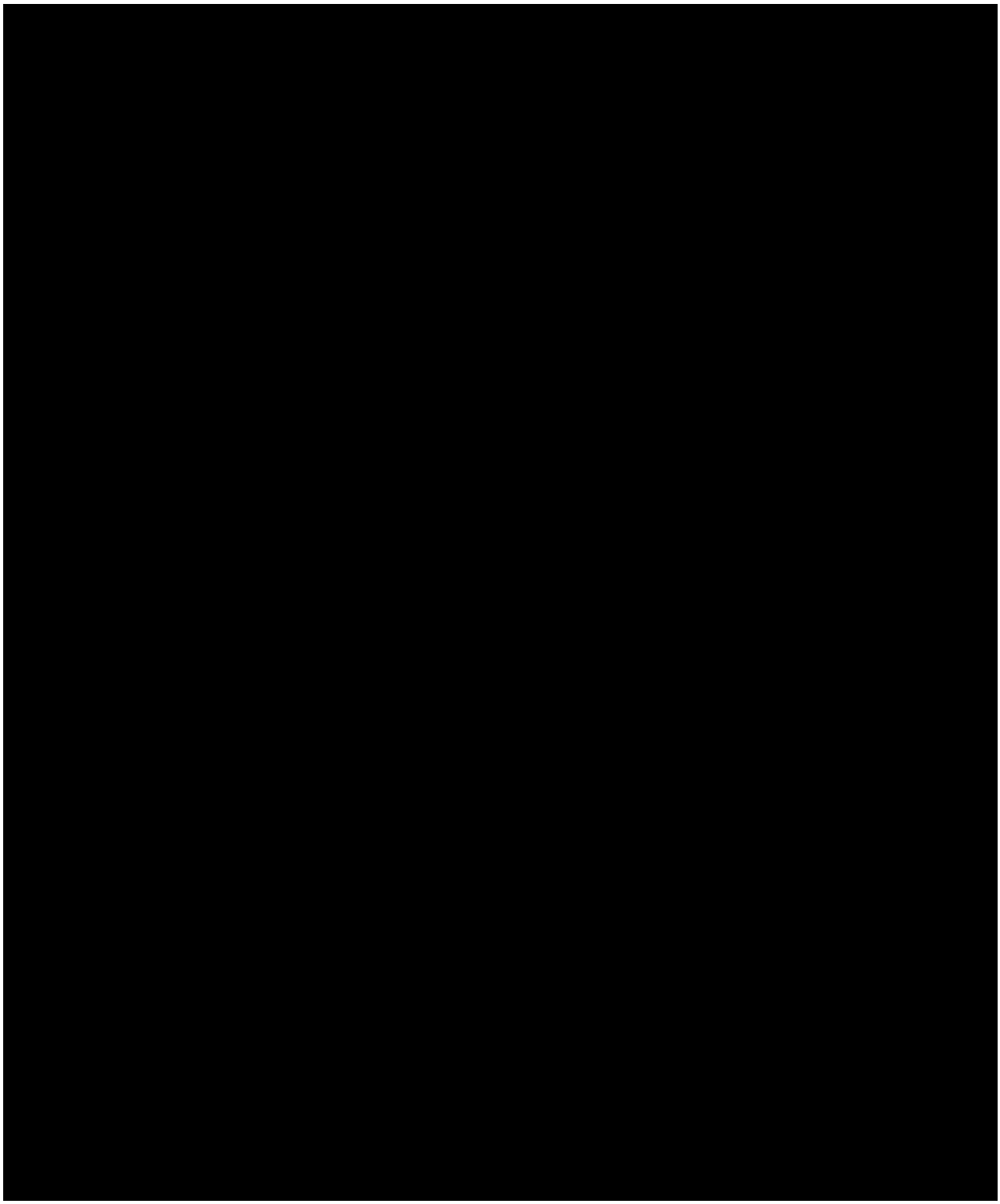
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g., prior to starting any of the procedures described in the protocol)
Period	A portion of the study which serves a specific purpose. Typical periods are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”
Rescue medication	Rescue medication is defined as medication used to control symptoms that are not adequately controlled on investigational and other study treatment. Rescue medication include: artificial tears and sialagogues (drugs promoting the flow of saliva) and NSAIDs
First-dose Pre-medication	Methylprednisolone (250 mg i.v.) prior 1st dose of VAY736 at Visit 101 and Methylprednisolone (125 mg i.v.) at Visit 201
Medication pack number	A unique identifier on the label of each investigational drug package
Period	A single time period of the study which contains different objectives, number of patients and treatment arms within the study
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy Study treatment only refers to VAY736 and placebo in this trial, with the exception of the first dose pre-medication which is also part of study treatment
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

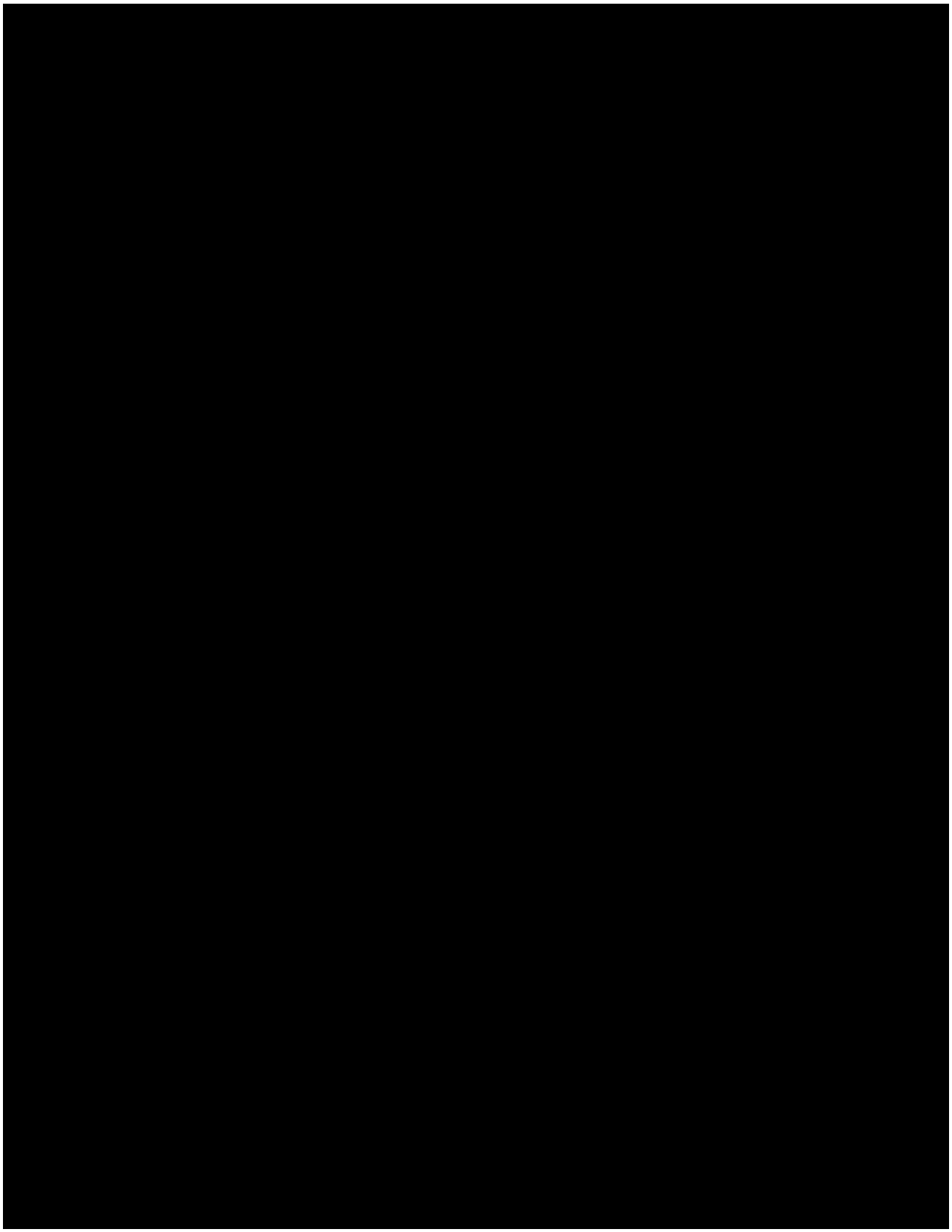


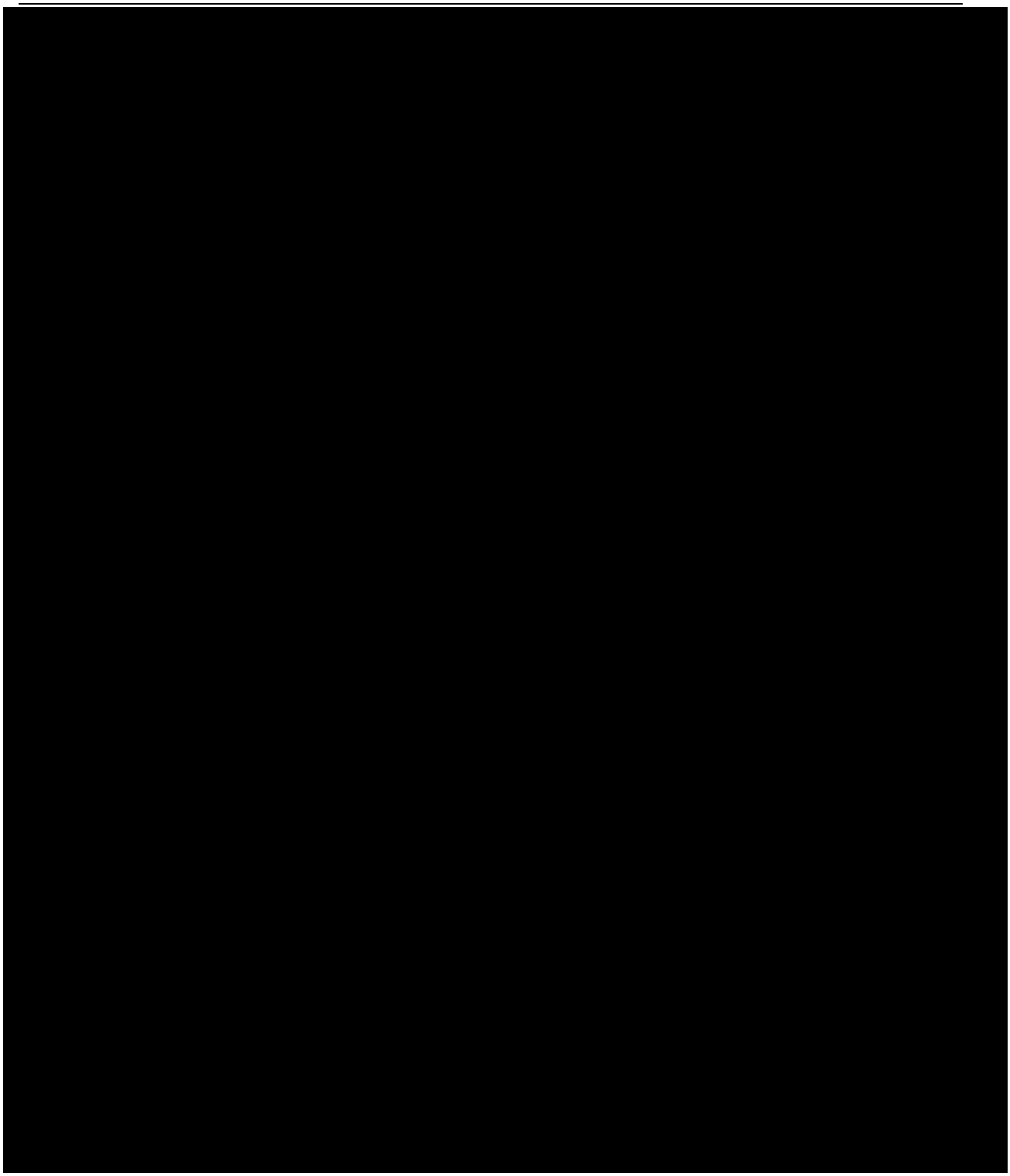












Protocol summary

Protocol number	VAY736A2201
Title	A randomized, double blind, placebo controlled multicenter Phase 2 dose- ranging study to assess the safety and efficacy of multiple VAY736 doses administered subcutaneously in patients with moderate to severe primary Sjögren's syndrome
Brief title	Study of safety and efficacy of multiple VAY736 doses in patients with moderate to severe primary Sjögren's Syndrome (pSS)
Sponsor and Clinical Phase	Novartis Phase 2b
Investigation type	Biologic
Study type	Interventional
Purpose and rationale	To determine the dose-response relationship of VAY736 for key efficacy and safety parameters
Primary Objective	To demonstrate a dose response of VAY736 defined as change in ESSDAI from baseline at 24 weeks
Secondary Objectives	To assess a dose response of VAY736 in the change from baseline of ESSPRI at 24 weeks To assess a dose response of VAY736 in the change from baseline of the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) at 24 weeks To assess changes from baseline in PhGA of the patient's overall disease activity at week 24 To assess a dose response of VAY736 in the change from baseline of SF-36 at 24 weeks To evaluate the effects of VAY736 on salivary gland function at 24 weeks [redacted] To assess safety and tolerability of VAY736 through incidence of AEs, SAEs, and monthly safety laboratory tests To assess immunogenicity (IG) of VAY736 by measuring serum anti-VAY736 antibodies To assess PK of VAY736 after multiple s.c. doses at multiple time points
Study design	This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group trial in patients with active pSS. The study treatment period will last for 24 weeks and for a subset of patients up to 52 weeks. A post treatment safety follow up period for all patients will last for a minimum of 20 weeks.
Population	The study population will consist of male and female patients aged 18 to 75 years with pSS defined according to the revised American European Consensus Group (AECG) classification criteria, and having moderate to severe active disease. Approximately 180 patients are planned to be randomized worldwide
Key Inclusion criteria	• Male and female patients aged 18 to 75 years • Fulfilled revised American European Consensus Group criteria for pSS

	• ESSDAI value ≥6 at baseline, based on weighted scores of the 7 domains: biologic, hematologic, articular, cutaneous, glandular, lymphadenopathy and constitutional • ESSPRI value ≥5 at baseline • Seropositive at screening for anti-Ro/SSA antibodies • Stimulated whole salivary flow rate at screening of >0.1 mL/min

Key Exclusion criteria	• Secondary Sjögren's syndrome (presence of another connective tissue disease)
	• Use of other investigational drugs within 5 half-lives of enrollment or within 30 days whichever is longer, or longer if required by local regulations
	• Prior use of any B-cell depleting therapy (e.g., rituximab or other anti-CD20 mAb, anti-CD22 mAb or anti-CD52 mAb)
	  • within 1 year prior to randomization
	  • or as long as B-cell count <50 cells/µL
	• Current use of prednisone >10 mg/day [or equivalent other corticosteroid] or dose change within 2 weeks prior to randomization
	• Prior treatment with any of the following within 180 days prior to randomization (anti-BAFF mAb; CTLA4-Fc Ig (abatacept); anti-TNF-α mAb; intravenous/subcutaneous immunoglobulin (Ig); plasmapheresis; i.v. or oral cyclophosphamide; oral cyclosporine
	• Active viral, bacterial or other infections requiring systemic treatment at the time of screening or enrollment, or history of recurrent clinically significant infection or of bacterial infections with encapsulated organisms
	• Receipt of live/attenuated vaccine within a 2 month period before baseline
	• Positive hepatitis B, hepatitis C, HIV or tuberculosis test results at screening

Study treatment	<u>Study period 2:</u> Treatment arm 1: s.c. VAY736 for 24 weeks Treatment arm 2: s.c. VAY736 for 24 weeks Treatment arm 3: s.c. VAY736 for 24 weeks Treatment arm 4: s.c. placebo for 24 weeks <u>Study period 3:</u> Treatment arm 5: Previously placebo-treated patients (treatment arm 4) will receive s.c. VAY736 for 28 weeks Treatment arm 6: s.c. VAY736 for 28 weeks Treatment arm 7: s.c. placebo for 28 weeks.
Efficacy assessments	Clinical efficacy measurements related to primary and secondary objectives include components of the ESSDAI and of the ESSPRI, SF-36, FACIT-F, Visual analog scale (VAS) of the PhGA of overall disease activity, and salivary flow assessments
Key safety assessments	Clinical safety measurements include physical examination, vital signs, ECG, hematology, chemistry, anti-drug antibodies, [redacted], monitoring of IgM and IgG levels, pregnancy evaluation, collection of AEs, SAEs and injection reactions.

Data analysis	The dose response relationship among VAY736 and placebo will be characterized with regards to the change from baseline in ESSDAI at week 24. The generalized MCP-Mod methodology will be implemented using ESSDAI measurements from all time points until week 24 to confirm an overall dose-response signal, and to estimate the optimum dose that corresponds to the clinically relevant effect over placebo. Testing will be done at one-sided 5% alpha level. The key secondary variables (including change from baseline in ESSPRI, FACIT-F, SF-36, PhGA, PaGA and salivary flow over 24 weeks) will be analyzed using a MMRM including treatment, visit, treatment by visit interaction, stratification factor, baseline ESSDAI score and geographic region as fixed factors as well as the baseline value of variable analyzed as a covariate. The estimated means per dose and visit will be derived together with the 2-sided 95% confidence intervals. No hypothesis testing will be done for the secondary variables.
Keywords	Primary Sjögren's Syndrome, pSS, B-cell depleting therapy, BAFF receptor inhibitor, ESSDAI, dose-ranging, dose-response, monoclonal antibody, dryness, fatigue, autoimmune disease, sicca syndrome

1 Introduction

1.1 Background

Primary Sjögren's Syndrome (pSS) is a chronic autoimmune disease of unknown etiology, characterized by lymphoid infiltration and progressive destruction of exocrine glands. Although primarily organ-specific for the lacrimal and salivary glands, the inflammatory process can target any organ (Asmussen 1996). Thus, the clinical features range from dryness, pain and fatigue affecting nearly all patients, to severe, extra-glandular and systemic involvement in a more limited subset. The increased B-cell activity underlying pSS also results in an increased risk for malignant transformation, with lymphoma development occurring in up to 5% of Sjögren's syndrome patients (Ramos-Casals et al., 2005; Theander et al., 2011). Primary Sjögren's syndrome is second only to rheumatoid arthritis (RA) in prevalence as a systemic autoimmune disease, with an estimated prevalence of 0.2-0.5%. The disease affects mainly women with a female/male ratio of 9:1 and can occur at any age (Qin et al., 2015).

Current standard-of-care (SoC) treatment for pSS patients is limited to symptomatic care for the mucosal signs and symptoms (dryness). Steroids and conventional disease modifying antirheumatic drugs (DMARDs), although used in selected patients, have not been proven efficacious, and no pharmacologic intervention is effective against the severe, disabling fatigue. Hence, there are no approved treatments available for moderate to severe (i.e., systemic) pSS. B-cell depletion therapy using the anti-CD20 monoclonal antibody (mAb) rituximab may improve signs and symptoms for both glandular and extra-glandular manifestations of pSS as well as for lymphoma management. However, data derived from small cohorts have yielded mixed or inconsistent results, and additional studies are required. An initial study using another B-cell targeting approach, the B-cell activating factor (BAFF) antagonist belimumab did not show convincing effects at early time points, whereas one year data suggest limited efficacy on some relevant endpoints (EULAR Sjögren's syndrome Disease Activity Index [ESSDAI], EULAR Sjögren's Syndrome patient reported index [ESSPRI] and markers of B-cell hyperactivity), but not on the Short Form-36, fatigue, salivary gland flow and Schirmer's test (Mariette 2015).

ianalumab is a human monoclonal antibody (mAB) of type IgG1/κ binding to BAFF-receptor (BAFF-R). [redacted]

PK and Safety: The PK, safety and tolerability of ianalumab has been evaluated in phase 1 and 2a studies. [redacted]

As of June 30, 2016, 116 patients were enrolled into the ianalumab clinical program, of which a total of 101 patients received ianalumab, 86 received single doses of ianalumab, and twelve RA patients and three CLL patients received multiple doses of ianalumab.

Clinically, acute infusion reactions (CTCAE 4.03 grade 1-2) as a consequence of ADCC and unrelated to dosage, were the most important safety finding next to upper respiratory tract infections observed in previous clinical studies [redacted]
This short-term preliminary safety profile is considered adequate to continue development of ianalumab in pSS.

[redacted]

1.2 Purpose

The purpose of the current study is 2-fold: (i) to determine the dose-response relationship of ianalumab for key efficacy and safety parameters in order to define the most appropriate dose(s) for subsequent clinical studies (i.e., phase 3), and (ii) to evaluate which clinical endpoint(s) and/or scoring systems best characterize the multidimensional features of pSS.

2 Study objectives and endpoints

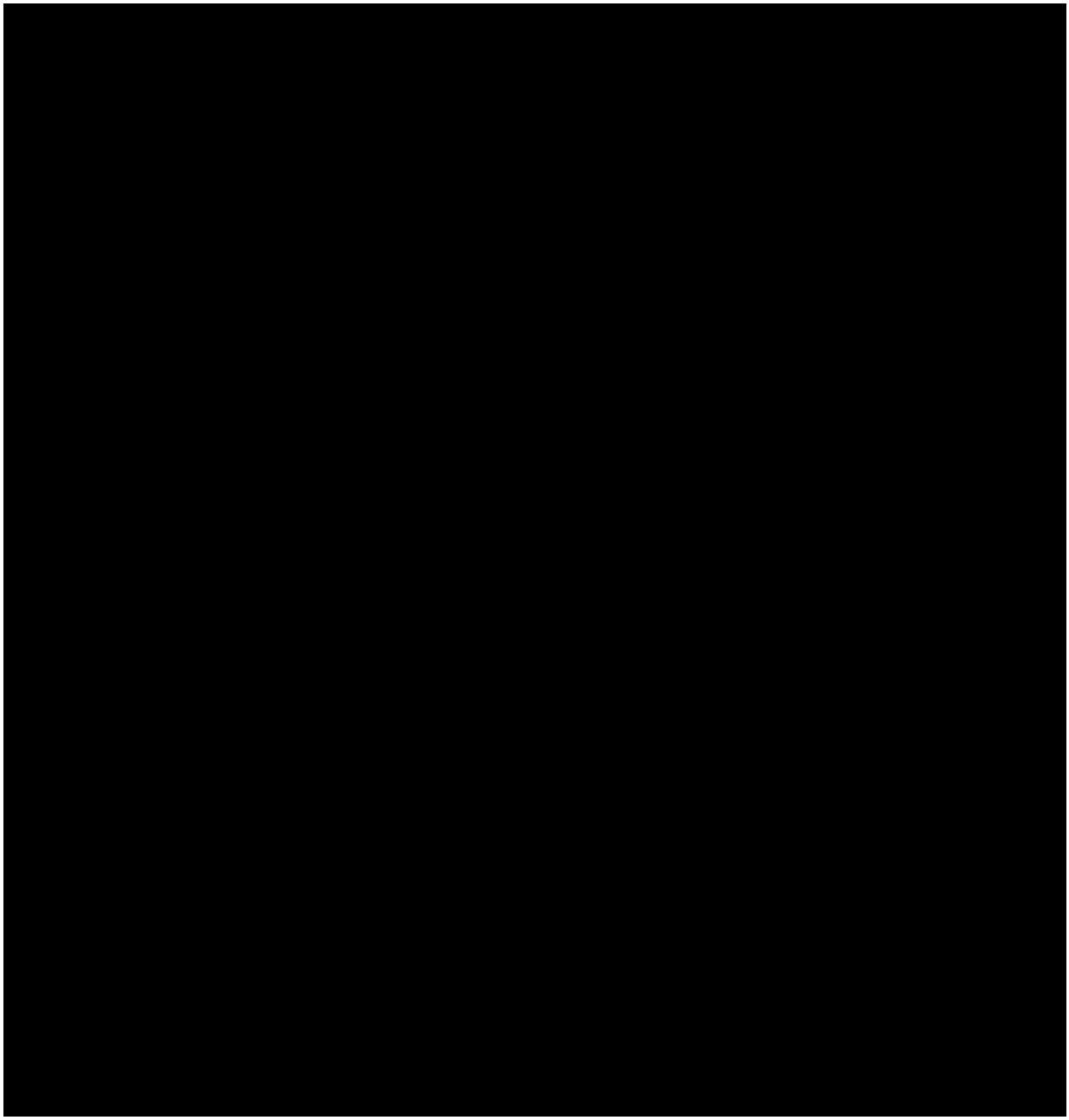
2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To demonstrate a dose response of VAY736 defined as change in ESSDAI from baseline at 24 weeks	Change in ESSDAI score from baseline over 24 weeks as compared to placebo	Section 9.4
Secondary		
To assess a dose response of VAY736 in the change from baseline of ESSPRI at 24 weeks	Change in ESSPRI score from baseline over 24 weeks as compared to placebo	Section 9.5
To assess a dose response of VAY736 in the change from baseline of the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) at 24 weeks	Change in FACIT-F from baseline over 24 weeks as compared to placebo	
To assess a dose response of VAY736 in the change from baseline of SF-36 at 24 weeks	Change in SF-36 physical component (PCS) and mental component (MCS) from baseline	

Objective	Endpoint	Analysis
	over 24 weeks as compared to placebo	
To assess changes from baseline in PhGA of the patient's overall disease activity at week 24	Change from baseline in PhGA of patient's overall disease activity (recorded by VAS) over 24 weeks as compared to placebo	
To assess change from baseline of ESSDAI, ESSPRI, PhGA, PaGA, FACIT-F, SF-36 at weeks 4, 8, 12 and 16.	Change in ESSDAI, ESSPRI, PhGA, PaGA, FACIT-F, and SF-36 from baseline at weeks 4, 8, 12, and 16 as compared to placebo	
To evaluate the effects of VAY736 on salivary gland function at 24 weeks	Change from baseline in salivary flow rate (unstimulated and stimulated) at 24 weeks as compared to placebo	
[redacted]	[redacted]	
To assess safety and tolerability of VAY736	AEs, SAEs, and routine safety laboratory tests	
To assess immunogenicity (IG) of VAY736	Serum anti-VAY736 antibodies (ADA assay) during treatment and follow up period	
To assess PK of VAY736 after multiple s.c. doses	Monthly and follow up PK measurements at the four dose levels	

[redacted]



3 Investigational plan

3.1 Study design

This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group trial in approximately 180 patients with active pSS. The study is divided into 4 study periods:

Period 1: A screening period of 4 weeks to assess patient eligibility. Patients can be re-screened only once and no study-related re-screening procedure should be performed prior to written re-consent by the patient.

Period 2: At baseline, eligible patients will be randomized to one of three VAY736 dose arms (VAY736 5 mg, 50 mg or 300 mg s.c.) or a placebo arm. Blinded study drug will be administered every four weeks for a 24-week period. Approximately 45 patients will be randomized per treatment group. [redacted], randomization will be stratified by:

- baseline ESSDAI score (<10 or ≥10 based on weighted scores)

[redacted]

The primary endpoint will be assessed at the end of period 2 (week 24).

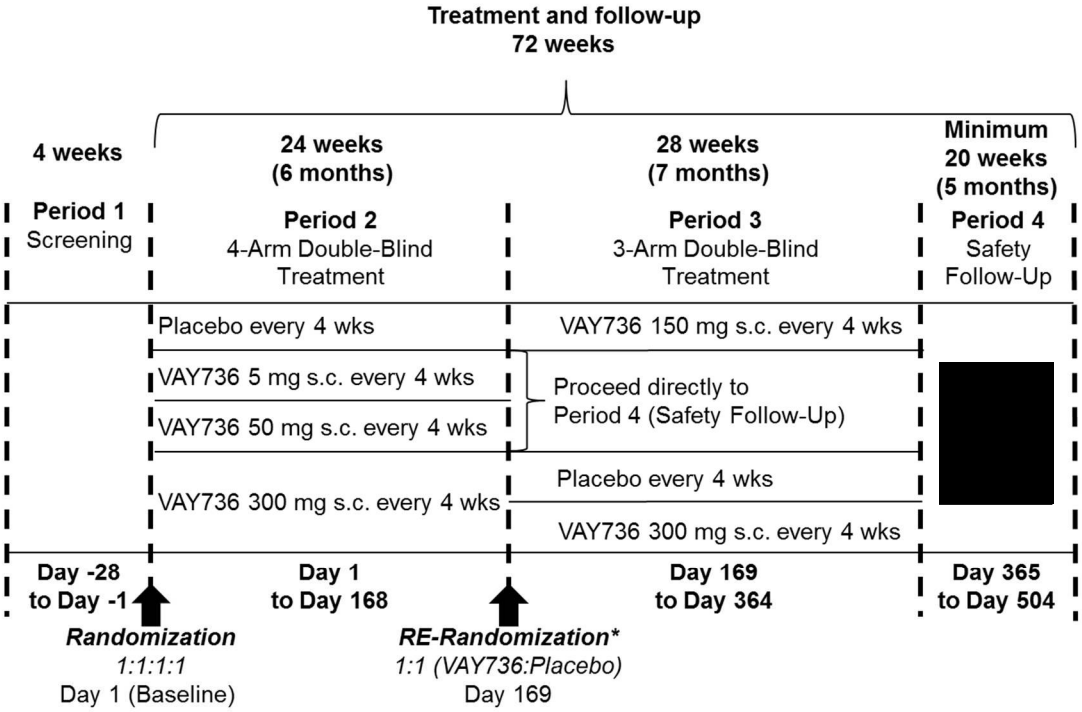
Treatment assignment in period 2 will remain double blinded until the end of period 3.

Period 3: After week 24 assessments, patients in the VAY736 300 mg arm will be re-randomized in a 1:1 ratio to either continue VAY736 300 mg s.c. every four weeks or switch to [redacted] placebo up to week 52. Patients who received placebo during period 2 will be switched to VAY736 150 mg s.c every four weeks up to week 52. Patients who received 5 mg and 50 mg s.c. in period 2 will proceed directly to period 4. Treatment assignment in period 3 will remain double blinded until the end of the study period.

Period 4: The safety follow-up period lasts for a minimum of 20 weeks from last dose administration of VAY736, or longer (with reduced visit frequency) [redacted] Patients who will be treated with another immunmodulatory or immunsuppressive treatment (e.g. azathioprine, cyclophosphamide, high dose glucocorticosteroids) after completion of the minimum 20 week safety follow-up period are excluded from further safety follow-up.

The primary efficacy analysis will be performed when all patients have completed the week 24 study visit. An interim analysis will occur when approximately 100 patients have completed their Week 24 visit.

Figure 3-1 Study design



**Only patients in the period 2 VAY736 300 mg arm will be eligible for period 3 re-randomization. Patients who were randomized to Pbo in period 2 will receive double blind VAY736 150mg s.c. every 4 weeks, but will not be re-randomized in period 3. All other patients will proceed directly from period 2 to period 4 (Safety Follow-Up period).*

3.2 Rationale for study design

The 24-week randomized, placebo-controlled design was previously executed in interventional phase 2 pSS studies (Mariette 2015, Bowman 2015, Devauchelle-Pensec 2015). The 24-week blinded treatment period is justified in this indication because pSS is a slowly progressing disease, placebo is given on top of standard treatments for sicca syndrome and no approved, systemic therapy for pSS exists. Further, patients receiving placebo in period 2 will be switched to active treatment in period 3. Established standard of care treatments for pSS include local remedies such as pilocarpine to control sicca symptoms, and in some patients systemic medication such as low-dose steroids, hydroxycholoroquine or methotrexate.

At the 24-week time point, patients who were on 300 mg VAY736 will be re-randomized to enter a second treatment period (period 3). To offer to patients who were being treated with placebo in period 2 the potential benefits of VAY736 treatment, these patients will receive double blind treatment with 150 mg s.c. VAY736 every 4 weeks in period 3. As patients from the dose arms 5 mg and 50 mg VAY736 will receive no further treatment and enter period 4 directly, partial derivation of the treatment assignment during period 2 is unavoidable. However, patients entering period 3 will not know their current treatment assignment and not be able to fully derive whether they had been on the placebo or 300 mg dose arm in period 2. Patients

entering period 3 will receive either 300 mg VAY736 or placebo or 150 mg VAY736 every 4 weeks, and be fully blinded to their treatment allocation.

[redacted]

Period 4 allows off-treatment follow-up of all patients [redacted].

3.3 Rationale for dose/regimen, route of administration and duration of treatment

[redacted]

In the pSS PoC trial, 1x3 mg/kg i.v. showed efficacy signals at week 6 on relevant outcomes including ESSPRI, patient and physician global assessments, and the fatigue instrument MFI. Consistent trends were also seen in total ESSDAI. [redacted] In the clinical program so far (cut-off Jun 2016), there was no safety signal following 10 mg/kg i.v. single dose administration (corresponding to 700 mg i.v. or ~1400 mg s.c. for a 70 kg individual).

[redacted]

150 mg dose selection for subset of patient in period 3:

Patients who receive placebo in period 2 will be switched at week 24 to 150 mg VAY736 every four weeks. [redacted] Finally, dosing every 4 weeks will improve patient convenience compared to more frequent vists/dosing.

3.4 Rationale for choice of comparator

Placebo will be comparator treatment for VAY736. Current standard-of-care treatment for pSS patients is limited to symptomatic care for the mucosal signs and symptoms (dryness). Steroids and conventional DMARDs are largely ineffective, and no pharmacologic intervention is effective against the severe, disabling fatigue. Hence, there are no approved treatments available for moderate-to-severe (i.e., systemic) pSS.

3.5 Purpose and timing of interim analyses/design adaptations

The primary efficacy analysis will occur when all randomized patients have reached the week 24 time point, assessing the primary endpoint of this study. One interim analysis (IA) will occur when approximately 100 patients have reached the week 24 primary endpoint.

The purpose for this interim analysis may include any of the following features: 1) Stopping dose(s) for futility, 2) Blinded sample size re-assessment, 3) Determination that sufficient evidence exists based on the evaluation of the dose-response models evaluated, to accelerate Phase III planning activities prior to the primary efficacy analysis being performed. Further details will be provided in the DMC charter.

After the primary analysis for week 24, analysis for week 52 will occur. The purpose of this analysis is reporting of study results (interim CSR) when all patients have completed the week 52 visit (period 3), or have discontinued the study treatment earlier. [redacted]

[redacted]

A final study analysis will occur when all patients have completed their safety follow up and EOS visit.

3.6 Risks and benefits

Initially, patients have a 75% chance to be treated with a potentially efficacious treatment for a chronic disease with possible long term outcomes including serious disabilities. Patients who receive placebo up to week 24 in period 2 will receive active treatment with VAY736 in period 3. Patients who are on placebo in period 2 and are being discontinued prior to week 24 for any reason will not be eligible to receive active treatment in period 3. The study is designed to limit exposure to placebo. However, for the 25% of patients who will receive placebo in period 2, no other approved systemic therapy exists, and thus i) certain background therapy is allowed during the trial and ii) in period 3, the opportunity of receiving active treatment.

As VAY736 is a systemic immunosuppressive treatment, the study population will be limited to include patients with moderate-to-severe pSS who are most likely to benefit from such a therapy. Based on a risk/benefit evaluation it was concluded that very severely ill patients with high steroid requirements (>10 mg/day prednisone or equivalent) or in need of immunosuppressive treatments such as cyclophosphamide, should not be included in this first multiple dose study of VAY736 in pSS. Hence, these medications are disallowed to be used concomitantly (Table 5-1).

[redacted]

Acute injection reactions: First-dose mild-to-moderate injection reactions were observed in the phase 1/2a studies in a substantial subset of patients. [redacted]

[redacted] Therefore, [redacted] a mandatory pre-medication with i.v. methylprednisolone (with or without additional antihistamine and/or paracetamol medication at the discretion of the investigator) prior to the first VAY736 dose will be administered in the current trial.

Infections: At the time of protocol amendment, no SAEs related to infections have been observed in VAY736 exposed patients (during/after VAY736 exposure) in the ongoing or completed VAY736 clinical trials. An increase in mild-to-moderate upper respiratory tract infections compared to placebo has been associated with use of VAY736. [redacted]

Neutropenia: [redacted] Late onset neutropenia (LON) [redacted] So far, no cases of LON were observed in VAY736 exposed patients after dosing.

Monitoring: Patients are required to stay at the clinic until at least 6 hours after first study medication (particular requirements for Japan; Section 5.5). Patients should be clinically monitored during this period. Patients should be instructed to promptly report symptoms occurring within 24 hours after study drug administration.

Potential safety risks will be monitored by routine assessments, including complete physical examination (with emphasis on salivary/parotid gland and lymph node assessments in the head/neck region, and inspection of the mouth including teeth and gums), and standard laboratory assessments to occur at all scheduled site visits (every 4 weeks). No specific safety monitoring measures beyond routine monitoring will be taken, [redacted] In the current trial, the safety assessments selected are standard for this indication and patient population. In addition, IgG and IgM levels will be monitored in regular intervals. [redacted]

Allergic reactions: Although no allergic reactions following i.v. or s.c. administration were observed so far, the potential to develop an allergic reaction in a predisposed subject cannot entirely be ruled out. Routine monitoring as for other biological treatments is warranted, as described in IB.

Vaccinations: In immune suppressed patients, live vaccinations may cause serious adverse events and vaccination success may be attenuated. No data exists on the effect of VAY736 on response to vaccinations in general. Study subjects should receive appropriate vaccinations

before entering the study in accordance with current immunization guidelines at least 4 weeks prior to study medication administration, noting that randomization should not occur less than 2 months after a live vaccine is given. For further information please refer to Vaccination Guidance for VAY736 (provided to study sites).

Although no signs and symptoms of immunogenicity have been observed so far, administration of mAb, independent of the antibody specificity for antigen, carries the risk of immune reactions such as acute anaphylaxis, serum sickness and the generation of anti-drug antibodies. Other clinical manifestations can include local skin reactions at the injection site, pyrexia and an influenza-like syndrome.

Potential side-effects of the methylprednisolone pre-medication are short-term and may include sodium retention-related weight gain and fluid accumulation, hyperglycemia and glucose intolerance, hypokalemia, gastrointestinal upset. These symptoms are generally self-limiting and do not require treatment. Patients with uncontrolled diabetes or hypertension will be excluded from the trial to avoid any risk in these patients.

The risk for patients in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, and compliance with criteria for treatment interruption outlined in the protocol. Drug-drug interactions are unlikely with biologics, however, sites and patients must strictly observe and adhere to the list of prohibited medications listed in the protocol (Section 5.5.8).

4 Population

The study population will consist of male and female patients aged 18 to 75 years with pSS defined according to the revised American European Consensus Group (AECG) classification criteria (Vitali et al., 2002), and moderate to severe active disease defined as: (i) having an ESSDAI score ≥6 within the following 7 domains: biologic, hematologic, articular, cutaneous, glandular, constitutional and lymphadenopathy (a subset of at least 30% of patients must have an ESSDAI ≥10). Patients also having involvement of one or more of the remaining five domains are eligible. Eligible patients must fulfill all inclusion and exclusion criteria. The goal is to randomize a total of approximately 180 patients at approximately 90 centers worldwide, including North America and Europe. Since a 50% screening failure rate is expected, approximately 360 patients will be screened.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent (IC) must be obtained before any assessment is performed
2. Male and female patients aged 18 to 75 years
3. Fulfilled revised American European Consensus Group criteria for pSS (Vitali et al., 2002); if key inclusion criteria are missing from medical history, information will be obtained at screening and may be used as a baseline value if required
4. ESSDAI value ≥6 at screening, based on weighted scores of the 7 domains: biologic, hematologic, articular, cutaneous, glandular, lymphadenopathy and constitutional domains
5. ESSPRI value ≥5 at baseline
6. Seropositive at screening for anti-Ro/SSA antibodies
7. Stimulated whole salivary flow rate at screening of >0.1 mL/min
8. Able to communicate well with the investigator, to understand and comply with the requirements of the study

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Use of other investigational drugs within 5 half-lives of enrollment or within 30 days whichever is longer, or longer if required by local regulations
2. Secondary Sjögren's syndrome (presence of another connective tissue disease)
3. Prior use of any B-cell depleting therapy (e.g., rituximab or other anti-CD20 mAb, anti-CD22 mAb or anti-CD52 mAb)
   - within 1 year prior to randomization
   - or as long as B-cell count <50 cells/μL
4. Current use of prednisone >10 mg/day [or equivalent other corticosteroid] or dose change within 2 weeks prior to randomization
5. Prior treatment with any of the following within 180 days prior to randomization (anti-BAFF mAb; CTLA4-Fc Ig (abatacept); anti-TNF-α mAb; intravenous/subcutaneous Ig; plasmapheresis; i.v. or oral cyclophosphamide; oral cyclosporine
   - Patients taking either hydroxychloroquine or methotrexate or azathioprine at consistent dose for ≥3 months prior to randomization are eligible if dose is maintained throughout the study
   - If azathioprine is discontinued prior to enrollment, a minimum washout period of 30 days prior to randomization is required.
6. Active viral, bacterial or other infections requiring systemic treatment at the time of screening or enrollment, or history of recurrent clinically significant infection or of bacterial infections with encapsulated organisms
7. History of major organ, hematopoietic stem cell or bone marrow transplant

8. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (e.g., mAb of IgG1 class) or to any of the constituents of the study drug (sucrose, L-Arginine hydrochloride, L-histidine, polysorbate 80, hydrochloric acid)
9. Required regular use of medications known to cause dry mouth/eyes as a regular and major side effect
10. Receipt of live/attenuated vaccine within a 2 month period before baseline
11. History of primary or secondary immunodeficiency, including a positive HIV (ELISA and Western blot) test result
12. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin, *in situ* cervical cancer or pSS related lymphoma), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
13. History of sarcoidosis
14. Any one of the following screening values of CBC laboratory values: Hemoglobin levels below 8.0 g/dL; Total leukocyte count less than 2,000/µL; Platelets <100.0 x 10^9/L; Absolute neutrophil count (ANC) <1.5 x 10^9/L (one re-test is allowed during the screening period)
15. Any surgical, medical (e.g., uncontrolled hypertension, heart failure or diabetes), psychiatric or additional physical condition that the Investigator feels may jeopardize the patient in case of participation in this study
16. Positive hepatitis B surface antigen (HBsAg), antiHB core antigen (anti-HBc) or anti-HB surface antigen (anti-HBs) or positive hepatitis C test result (Patients positive for anti-HBs after Hep B vaccination but negative for HBsAg and anti-HBc are eligible; Table 19-1)
17. Evidence of active tuberculosis (TB) infection (after anti-TB treatment, patients with history of or latent TB may become eligible according to national guidelines)
18. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
19. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 4 months after stopping of investigational medication.

    Highly effective contraception methods include:

    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    c. Male sterilization (at least 6 months prior to screening and confirmed as successful). For female patients in the study, the vasectomized male partner should be the sole partner for that patient
    d. Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system

(IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Investigational drug: VAY736 powder for solution for infusion/injection (lyophilizate in vial) 150 mg per 6 mL glass vial. Each vial contains nominally 150 mg VAY736 as a lyophilized cake. The vials contain a 20% overfill to ensure a complete withdrawal of the required amount of VAY736. VAY736 150 mg Powder for Solution is suitable for subcutaneous administration.

Immediately prior to administration, water for injection (WFI) is added to the vial and the powder is dissolved. Since VAY736 is a protein, the reconstituted vials may contain a few translucent particles.
Generic placebo: liquid placebo (platform placebo), for s.c. injections.

5.1.2 Additional treatment

Pre-medication

In order to prevent injection reactions and inadvertent unblinding, all patients should receive the following pre-medication regimen only for the first injection of study drug in period 2 provided by the study center:

- 250 mg methylprednisolone approx. 1 hour pre-dose as an i.v. bolus injection or infusion (a time window of +/- 30 min is allowed)
- At the investigator's discretion, in addition to methylprednisolone, paracetamol (acetominophen) at doses not exceeding 1000 mg p.o. and/or oral second generation antihistamines (e.g., loratadin) may be administered

In period 3, the following pre-medication regimen will be followed for the first administration of study drug, provided by the study center:

- 125 mg methylprednisolone approx. 1 hour pre-dose as an i.v. bolus injection or infusion (a time window of +/- 30 min is allowed)

- At the investigator's discretion, in addition to methylprednisolone, paracetamol (acetominophen) at doses not exceeding 1000 mg p.o. and/or oral second generation antihistamines (e.g., loratadin) may be administered

The rationale for the lower methylprednisolone dose in period 3 is to assess whether this lower dose is also sufficiently effective in preventing injection reactions.

Other

Other additional treatment may include standard of care for dry eye and dry mouth symptoms, such as the use of artificial tears and artificial saliva/salivary stimulants (e.g., cevimeline, pilocarpine) at the discretion of the treating physician. Amount and frequency of use should be recorded at each visit. Please refer to Table 5-1 for guidance on suggested treatment time pause prior to assessment of clinical disease outcome measurements. Artificial tears and artificial saliva are to be provided by the study center or personal physician.

Table 5-1 Dry eye/dry mouth treatment time pause prior to study assessments

TREATMENT TYPE	TIME INTERVAL
Artificial tears	4 hrs
Opthalmic cyclosporine (Restasis)	24 hrs
Artificial saliva	4 hrs
Pilocarpine	12 hrs
Cevimeline or other salivary stimulants	24 hrs or 5x times half-life whichever is longer

Azathioprine (up to 150 mg/day), Methotrexate (≤25 mg/week), hydroxychloroquine (≤400 mg/day) are allowed as stable background medication defined as continued treatment ≥3 months without dose adjustments. Low-dose steroids (prednisone or equivalent ≤10 mg/day) is allowed and patients must be on a stable dose for at least 2 weeks prior to randomization. Refer to Section 5.5.8 for prohibited medication/doses.

5.2 Treatment arms

Patients will be assigned at baseline to one of the following 4 treatment arms in a ratio of 1:1:1:1 for 24 weeks in period 2.

- Double blind VAY736 - 300 mg s.c. administration every 4 weeks
- Double blind VAY736 - 50 mg s.c. administration every 4 weeks
- Double blind VAY736 - 5 mg s.c. administration every 4 weeks
- Double blind Placebo s.c. administration every 4 weeks

Patients who were in the placebo arm in period 2 will switch to the following treatment arm in period 3:

- Double blind VAY736 - 150 mg s.c. administration every 4 weeks

At the end of period 2, patients from the VAY736 300 mg every 4 weeks arm will be re-randomized to either i) double blind VAY736 300 mg every 4 weeks or ii) may start receiving double blind placebo every four weeks.

5.3 Treatment assignment and randomization

At baseline all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. Mis-randomized patients are defined as cases where IRT randomization was performed by the site by mistake and study kit numbers were not communicated to the unblinded pharmacist and no study medication was prepared for administration. Mis-randomized patients will not be re-screened.

At the end of period 2, patients randomized to 300 mg VAY736 and completed treatment period 2, will be randomized a second time (re-randomization) by the IRT system to receive 300 mg VAY736 or placebo in period 3. Patients previously on placebo in period 2 will start receiving 150 mg VAY736 (without randomization). All above described doses will be blinded.

The IRT will assign a randomization number (and re-randomization if applicable) to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization and re-randomization numbers will not be communicated to the caller.

All randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

[redacted], randomization at baseline will be stratified by:

1. baseline ESSDAI score (≥10 or <10 based on weighted scores)

[redacted]

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Group.

5.4 Treatment blinding

Patients, investigator staff and persons performing the assessments, will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: randomization office and the Data Monitoring Committee (DMC); (2) the identity of the treatments will be concealed by the use of study drug that are all identical in packaging, labeling, schedule of administration and amount of administrations per patient. The appearance of the placebo preparation, ready to administer to the patient, will be identical to that of active drug to maintain the blind. Placebo and active medication will be prepared by an un-blinded pharmacist

or qualified site personnel at each site. With this purpose the same materials and the same administration process should be followed for the placebo.

The designated Novartis clinical trial team members will be unblinded following database lock for the primary endpoint analysis and IA, to perform the analysis.

[redacted]

Unblinding will only occur in the case of patient emergencies (see Section 5.6) and at the conclusion of the study. At the time of any interim analyses (see Section 9.7), only the Novartis clinical team will be unblinded to study results. Patients and investigators will remain blinded to their treatment arms in period 2. Inherently to the study design, partial derivation of dosing received in period 2 may occur as patients enter period 3/4.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject/Patient Number (Patient ID) which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject/Patient Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the CRF book with a matching Subject/Patient Number from the EDC system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the ‘Screening period Study Disposition’ CRF.

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g., the second patient is assigned patient number 2, the third patient is assigned patient number 3). The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. For studies using eCRFs, only the assigned patient number must be entered in the field labeled “Patient ID” on the data entry screen (e.g., enter ‘1’, ‘2’, etc.). Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Log, and the ‘Demography’ eCRF should also be completed.

5.5.2 Dispensing the study drug

The study drug packaging has a 2-part label. A unique randomization number is printed on each part of this label which corresponds to one of the "n" treatment arms and a specific visit. Investigator staff will identify the study drug package(s) to dispense by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

Study drug will only be dispensed to an unblinded pharmacist who will reconstitute VAY736 powder for solution and prepare the dilutions for subcutaneous injection.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

The pharmacist manual will be provided to investigational sites and contains detailed information on the reconstitution of VAY736 as well as preparation of different doses through dilution.

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by unblinded monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment (incl. pre-medication)

Methylprednisolone as pre-medication: the 'Dosage administration record - Methylprednisolone' eCRF is a specific eCRF for recording mehylprednisolone pre-medication. Any other medication given as pre-medication (paracetamol/antihistamines) will be recorded on the concomitant medications eCRF. All pre-medications will be supplied by the study site.

Please also refer to Section 5.5.6 (Rescue medication), Section 5.5.7 (Concomitant medication) and Section 5.5.8 (Prohibited concomitant medication).

Further details are described in the CRF completion guidelines.

5.5.4 Instructions for prescribing and taking study treatment

All kits of study treatment assigned by the IRT will be recorded/databased in the IRT.

Powder for solution:

VAY736 powder for solution for infusion/injection (lyophilizate in vial) 150 mg per 6 mL glass vial. Each vial contains nominally 150 mg VAY736 as a lyophilized cake. The vials contain a 20% overfill of to ensure a complete withdrawal of the required amount of VAY736. VAY736 150 mg Powder for Solution is suitable for subcutaneous administration.

Immediately prior to administration, water for injection (WFI) is added to the vial and the powder is dissolved. Since VAY736 is a protein, the reconstituted vials may contain a few translucent particles.

Solution for subcutaneous injection for all doses:

Reconstitute one VAY736 150 mg Powder for Solution for injection vial by slowly injecting 1.0 mL of WFI into the vial containing the lyophilized cake of VAY736. The stream of diluents should be directed onto the lyophilized cake. Then the vial is tilted by an angle of approximately 45° and gently rotated between the fingertips for 1 minute. Allow each vial to stand for 5 minutes at room temperature. Rotate each vial at an angle of about 45 degrees for about 1 minute. After around 15 minutes in total a clear to opalescent solution essentially free of visible particles is available (the VAY736 concentration is of 150 mg/mL in final a volume of 1.2 mL from which 1.0 mL can be withdrawn).

Dose administration:

The maximal dose which can be administered at once per single s.c. injection is 150 mg corresponding to 1.0 mL of the 150 mg/mL Solution for subcutaneous injection. For patients randomized to 300 mg dose, a second vial of VAY736 will be dispensed by IRT. The required number of vials will be prepared (1 vial for 5 mg, 50 mg and 150 mg doses, and 2 vials for 300 mg).

For blinding reasons, all patients will receive two injections. These injections must be administered in two different body locations (left/right thigh, left/right upper arm, abdomen). Injection sites must be alternated between visits.

- 5 mg dose arm (period 2): The unblinded pharmacist will make dilutions of the solution for s.c. injection as detailed in the pharmacist's manual. The patient will receive one injection of diluted solution for s.c. injection and one injection of generic placebo.
- 50 mg dose arm (period 2): The unblinded pharmacist will make the necessary dilution of the solution for s.c. injection as detailed in the pharmacist's manual. The patient will receive one injection of the diluted solution for s.c. injection and one injection of generic placebo.
- 150 mg dose arm (period 3): No dilutions are necessary for this dose level. The patient will receive 1 mL of solution for injection (as after reconstitution) and another injection of generic placebo.
- 300 mg dose arm (period 2 and period 3): IRT will dispense two vials of VAY736 powder for solution. The powder will be reconstituted and the patient will receive two injections of 1 mL each, 150 mg/mL VAY736 solution for s.c. injection.

Generic placebo:

Liquid placebo [redacted], for s.c. injections.

Please refer to the pharmacist's manual for further instructions on reconstitution and dilution of VAY736.

Please see Table 6-1 and 6-2 for scheduling of IRT contact and administration of study medication and pre-medication. Doses will be administered once every four weeks for 24 weeks in period 2 and once every four weeks for 28 weeks in period 3. The last doses administered in period 2 and 3 will occur on study scheduled visit 106 and 207, respectively.

For the first administration for all patients in period 2 and 3, the patient must remain at the study center for observation for at least 6 hours or longer as per local requirements. [redacted]

5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational drug dose adjustments are not permitted.

For patients who experience an adverse event which precludes administration of the study treatment, a maximum of 1 week dose delay is permitted to allow for recovery. For patients who are unable to tolerate the protocol-specified dosing scheme, a dose interruption of investigational drug is permitted in order to keep the patient on study drug. A maximum of one dose may be missed during each of period 2 and period 3.

Dosing can be brought forward or delayed by up to 1 week for administrative reasons. The subsequent dose should be given according to the original schedule (i.e., do not move subsequent dose dates).

These changes must be recorded on the 'Dosage Administration Record' eCRF.

5.5.6 Rescue medication

There is no established, approved immunosuppressive treatment for pSS. Patients may receive nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, or symptomatic care at the discretion of the treating physician as outlined in Section 5.1.2. Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started. If any of the medications listed in Table 5-2 is deemed necessary rescue therapy, the investigator must follow the actions to be taken outlined in this table. Rescue medicine is to be provided by the study center or personal physician. Patients must be encouraged to continue the safety follow-up period 4 as detailed in Table 5-3 even when discontinued permanently from study drug. However, patients who receive a disallowed immunomodulatory or immunosuppressive treatment will not be followed beyond the mandatory 20-week safety follow-up, [redacted]

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies eCRF. Use of NSAIDs, acetominophen, artificial tears/saliva and low dose steroids must be recorded on the 'Concomitant medications/Significant non-drug therapies' eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-2 is NOT allowed in study periods as indicated.

Table 5-2 Prohibited medication

Medication	Prohibited in Study Period	Action to be taken
Other experimental therapies	All	Study discontinuation required, patients should remain in the study and follow visit schedule of respective treatment period
Other biologics	All	Study discontinuation required, patient should remain in study and follow visit schedule of respective treatment period
DMARDs or other immune suppressive agents or changes in an existing DMARD regimen (hydroxychloroquine or methotrexate)	Period 2, Period 3	Study treatment discontinuation may be required on a case-by-case basis
Prednisone >10 mg [or equivalent other corticosteroid].	Period 2, Period 3	Study treatment discontinuation may be required on a case-by-case basis
Intravenous or oral cyclophosphamide; oral cyclosporine	All	Study treatment discontinuation required in periods 2 and 3. Patient should remain in the study and follow visit schedule of respective treatment period
Medications known to cause, as a major side effect, dry mouth/eyes, including e.g.1st generation antihistamines, certain antidepressants, anticholinergics, sedatives, antipsychotic drugs, anti-Parkinson agents	Period 2, Period 3	Study treatment discontinuation may be required on a case by case basis
Live/attenuated vaccine	Period 1 (within a 2 month period before baseline), Period 2, Period 3, and for 5 half-lives after	Study treatment discontinuation. Patient should remain in the study and follow visit schedule of respective treatment period

Medication	Prohibited in Study Period	Action to be taken
	discontinuation of investigational drug [redacted].	

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

In addition, oral and written information to the patient must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time. After a code break, the patient must remain in the study and may continue to receive study treatment.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol.

Continuing care should be provided by investigator and/or referring physician based on patient availability for follow-up. This care may include enrollment in an extension study, if any.

When the patient completed a minimum follow-up period of 20 weeks [redacted] the patients will undergo the End-of-Study visit within 4 weeks. [redacted] Patients who will be treated with another immunmodulatory or immunsuppressive treatment (e.g. azathioprine, cyclophosphamide, high dose glucocorticosteroids) after completion of the minimum 20 week safety follow-up period are excluded from further safety follow-up.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see Section 6.5.6 and Section 7.6)
- Use of prohibited treatment as per specifications in Table 5-2
- Any situation in which study participation might result in a safety risk to the patient
- Patient having received a live vaccine
- Adverse events, abnormal laboratory values or abnormal test result that indicate a safety risk to the patient. For liver or renal events, refer to Table 14-2 in Appendix 2.

In addition, in case of emergence of the following adverse events discontinuation must be considered jointly by the investigator and Novartis:

- Persistent neutropenia CTC grade 3 or higher that may preclude further administration of a B-cell depleting agent
- SAEs or severe AEs of infection

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. If a subject withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a subject's withdrawal from the study and record this information on the CRF. Patients that become pregnant during the study should be followed up as per the Assessment Schedule. The Investigator may determine whether any assessments should not be performed if they are considered to not be clinically appropriate, in conjunction with the patient's treating physician/obstetrician.

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The patient should continue to return to the clinic for the scheduled visits in the respective treatment period. If the patient decides to leave the study, a study treatment discontinuation visit must occur as soon as possible after actual discontinuation of the study drug. Treatment discontinuation visit assessments detailed in the "unscheduled treatment discontinuation visit" (TD) in Table 6-1 and Table 6-2 should be completed and recorded in the eCRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage Administration eCRF.

Patients who discontinue after having received at least one VAY736 administration and who do not complete the visits in the respective treatment period should return for the long-term safety follow up period 4. In period 4, visits are scheduled as outlined in Table 5-3 below [redacted]

Table 5-3 Outline of visit frequency in period 4

Visit frequency	TD period 2	TD period 3	No. of visits
Every 4 weeks	week 24 -week 40	week 52 - week 68	4 visits
Every 8 weeks	week 40 - week 56	week 68 - week 84	2 visits
Every 12 weeks	week 56 - week 80	week 84 - week 108	2 visits
Every 24 weeks	week 80- week 128	week 108 - week 156	2 visits

TD = Study treatment discontinuation

[redacted] The End-of-Study visit will include study completion evaluations followed by discharge from the study. Patients who discontinue during the safety follow up period will be asked to complete the end of study visit. For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9.

5.6.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

5.6.4 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrollment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the assessments are performed and should be documented in the eCRF. Assessments indicated with an "S" will only be documented at source.

Patients must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

In period 4, patients will have visits every four weeks for the mandatory 20-week safety follow-up period. [redacted]

Patients who are not willing to return to the site for follow up visits in period 4, will be contacted for safety evaluations during the 30 days following the last administration of study treatment.

Table 6-1 Assessment schedule for period 1 (Screening) and period 2 (Randomized treatment period)

Period	**Period 1: Screen**	**Period 2: Treatment**							**Notes**
Visit	**1**	**101 (BL)**	**102**	**103**	**104**	**105**	**106**	**199 / TD[7]**	[7]If patient discontinues treatment early, safety follow up period 4 will be entered after completion of this visit
Day	**-28**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	
Week	**-4**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	
Obtain informed consent (IC)	x								IC obtained prior to all study specific screening procedures
Demography	x								
Inclusion/exclusion	x	x							
Medical history	x								Section 4 specifies which I/E criteria are applicable for screening and/or baseline
Physical exam	S	S	S	S	S	S	S	S	
Height[1], weight, vital signs	x	x	x	x	x	x	x	x	[1]Height only collected at Screening
PhGA of overall disease activity	x	x	x	x	x	x	x	x	
ESSDAI	x	x	x	x	x	x	x	x	
Salivary flow, stimulated	x	x			x			x	
Salivary flow, [redacted]		x			x			x	
[redacted]									
ECG	x	x						x	
Biopsy	X[2]							X[2, 2A]	[2]Performing a biopsy for the substudy is optional at both screening and end of treatment [2A] Optional collection of archival tissue slides at end of treatment.
Randomization		S							
Pre-medication		x							
Dosage administration record		X[3]	x	x	x	x	x		[3]First dose of study medication can be adminsitered 1 calendar day after randomization
Contact IRT	S	S	S	S	S	S	S	S[4]	[4]IRT will confirm if patient will be treated in period 3 but not notify whether patient was re-randomized

Period	Period 1: Screen	Period 2: Treatment							Notes
Visit	**1**	**101 (BL)**	**102**	**103**	**104**	**105**	**106**	**199 / TD[7]**	[7]If patient discontinues treatment early, safety follow up period 4 will be entered after completion of this visit
Day	**-28**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	
Week	**-4**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	
Adverse Events	x	x	x	x	x	x	x	x	AEs include both serious and non-serious events
Renal/liver event monitoring	x	x	x	x	x	x	x	x	
Prior concomitant medications/procedures	x	x							
Concomitant medications/procedures		x	x	x	x	x	x	x	
Period completion/disposition form	x							x	
ESSPRI	x	x	x	x	x	x	x	x	
[redacted]									
FACIT-F, SF-36 PaGA of overall disease activity and patient diary[5]		x	x	x	x	x	x	x	[5]Diary is to be completed weekly by patient
[redacted]									
HIV, Hep B (HBsAg, anti-HBs, anti-HBc), Hep C	x								
TB (Quantiferon/PPD)	x								
Hematology and biochemistry	x	x	x	x	x	x	x	x	[redacted]
Serum pregnancy	x	x	x	x	x	x	x	x	
Urinalysis	x	x	x	x	x	x	x	x	
IgG, IgM	x	x	x	x	x	x	x	x	
[redacted]									
Pre-dose PK sample		x	x	x	x	x	x	x	
Immunogenicity		x			x			x	

Period	Period 1: Screen	Period 2: Treatment							Notes
Visit	**1**	**101 (BL)**	**102**	**103**	**104**	**105**	**106**	**199 / TD[7]**	[7]If patient discontinues treatment early, safety follow up period 4 will be entered after completion of this visit
Day	**-28**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	
Week	**-4**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	
[redacted]									

TD = Study treatment discontinuation; If patient withdraws consent (as per definition) and will not enter period 4, assessments from Table 6-3 PSD must be performed as well
X = assessment to be recorded on clinical data base
S = assessment to be recorded on source documentation only

Table 6-2 Assessment schedule for study period 3 (Extended treatment period) only for patients who continue treatment

Period	**Period 3: Extended Treatment**									**Notes**
Visit	**201**	**202**	**203**	**204**	**205**	**206**	**207**	**208**	**299 /TD[7]**	[7]If patient discontinues treatment early, safety follow up period 4 will be entered after completion of this visit
Day	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**339**	**364**	
Week	**24**	**28**	**32**	**36**	**40**	**44**	**48**		**52**	
Physical exam		S	S	S	S	S	S		S	
Weight, vital signs		x	x	x	x	x	x		x	
PhGA of overall disease activity		x	x	x	x	x	x		x	
ESSDAI		x	x	x	x	x	x		x	
Salivary flow (stimulated and unstimulated)		x		x			x			
Saliva sample		x		x			x			
[redacted]										
Local ECG				x					x	
[redacted]										
Re-randomization	S[3]									[3]IRT will confirm if patient will be treated in period 3 but not notify whether patient was re-randomized
Dosage administration record	x	x	x	x	x	x	x			
Pre-medication	x									
Contact IRT	S	S	S	S	S	S	S		S	
Adverse events		x	x	x	x	x	x		x	AEs include both serious and non-serious events
Renal/liver event monitoring		x	x	x	x	x	x		x	
Concomitant medications		x	x	x	x	x	x		x	
Period completion/disposition form									x	
ESSPRI, FACIT-F, SF-36, PaGA, patient diary[4]		x	x	x	x	x	x		x	[4]Diary is to be completed weekly by patient
[redacted]										

Period	Period 3: Extended Treatment									Notes
Visit	**201**	**202**	**203**	**204**	**205**	**206**	**207**	**208**	**299 /TD[7]**	[7]If patient discontinues treatment early, safety follow up period 4 will be entered after completion of this visit
Day	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**339**	**364**	
Week	**24**	**28**	**32**	**36**	**40**	**44**	**48**		**52**	
[redacted]										
Hematology and biochemistry		x	x	x	x	x	x		x	
Serum pregnancy		x	x	x	x	x	x		x	
Urinalysis		x	x	x	x	x	x		x	
IgG, IgM		x	x	x	x	x	x		x	
[redacted]										
Pre-dose PK sample		x	x	x	x	x	x			
Post-dose PK sample								x		72 hours post last dose follow up sample
Immunogenicity				x			x			
[redacted]										

TD = Study treatment discontinuation; If patient withdraws consent (as per definition) and will not enter period 4, assessments from Table 6-3 PSD must be performed as well
X = assessment to be recorded on clinical data base
S = assessment to be recorded on source documentation only

Table 6-3 Assessment schedule for study period 4 (safety follow-up period) for all patients

Period 4: Follow-up	**Mandatory follow-up visits**			**Conditional individualized follow-up visits**			**Manda -tory**	**Notes**
Visit	**301**	**302**	**303**[9]	**304**	**305 and 306**	**307, 308 and 309**	**399**[10]**/ PSD/ (EoS)**	[9]Marks 16 weeks of follow up: [redacted]
Study week for patients who completed period 3 treatment	**56**	**60**	**64**	**68**	**76 and 84**	**96, 108**[12] **and 132**	**156**[11]	[redacted] [12]Marks the 1 year follow up time point
Study week for patients who completed period 2 treatment	**28**	**32**	**36**	**40**	**48 and 56**	**68, 80**[12] **and 104**	**128**[11]	[redacted] [12]Marks the 1 year follow up time point
Physical exam	S	S	S	S	S	S	S	
Weight, vital signs	x	x	x	x	x	x	x	
ESSDAI	x	x	x	x	x	x	x	
Adverse events	x	x	x	x	x	x	x	AE include both serious and non-serious events
Kidney and liver event monitoring	x	x	x	x	x	x	x	
Concomitant medications	x	x	x	x	x	x	x	
Period completion/disposition form							x	
Hematology and biochemistry	x	x	x	x	x	x	x	[redacted]
IgG, IgM	x	x	x	x	x	x	x	
Urine pregnancy[14]	x	x	x	x	x	x		[14]Monthly tests at home during months without study visits until 1 year after TD or until EoS, whichever occurs earlier
Serum pregnancy							x	
Urinalysis	x	x	x	x	x	x	x	
Lipid[8]							x	[8]Lipid is collected from same sample as chemistry
[redacted]								
PK sample	x	x	x	x	x		x*	*Only for patients who prematurely withdraw

Period 4: Follow-up	**Mandatory follow-up visits**			**Conditional individualized follow-up visits**			**Manda -tory**	**Notes**
Visit	**301**	**302**	**303**[9]	**304**	**305 and 306**	**307, 308 and 309**	**399**[10]**/ PSD/ (EoS)**	[9]Marks 16 weeks of follow up: [redacted]
Study week for patients who completed period 3 treatment	**56**	**60**	**64**	**68**	**76 and 84**	**96, 108**[12] **and 132**	**156**[11]	[redacted] [12]Marks the 1 year follow up time point
Study week for patients who completed period 2 treatment	**28**	**32**	**36**	**40**	**48 and 56**	**68, 80**[12] **and 104**	**128**[11]	[redacted] [12]Marks the 1 year follow up time point
[redacted]								
Immunogenicity		x		x			x	

PSD = Premature subject/patient discontinuation; X = assessment to be recorded on clinical data base; S = assessment to be recorded on source documentation only

6.1 Information to be collected for screen-failed patients

All patients who have signed informed consent but not entered into the next period will have the study completion page for the screening period, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, ethnicity, source of patient referral, relevant medical history/current medical condition present before signing informed consent where possible, diagnoses and not symptoms will be recorded.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

The following assessments are to be done at screening only and will not be repeated after the patient starts with study treatment.

6.2.1 Screening for Hep B, Hep C and HIV

- All patients will be screened for hepatitis B surface antigen (HBsAg), anti-HBs, and anti-HBc. Patients testing positive for any of the serologic markers will not be eligible for randomization, with the exception of anti-HBs due to previous vaccination against Hep B. Table 19-1 in Appendix 7 provides detailed Hep B serology result interpretations.
- Screening for hepatitis C will be based on HCV antibodies.
- Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot.

Appropriate counseling will be made available by the Investigator in the event of a positive finding. Results will be available as source data and will not be recorded within the CRF.

All samples will be shipped to the central laboratory.

6.2.2 Screening for Tuberculosis

Determination of the tuberculosis (TB) status will be required before administration of study treatment and should be performed as defined by local guidelines. The TB status must be determined by medical history, signs, symptoms, TB testing (QuantiFERON-TB Gold assay or, if per local requirement only, a purified protein derivative [PPD] test may be performed instead of Quantiferon).

Quantiferon

If the test result is negative, the patient may be randomized.

If the test result is positive, the investigator should perform workup for the test result as per local procedures. If a TB workup was conducted prior to screening the patient, results of the

workup can be used to assess eligibility if the workup was conducted within 12 weeks prior to randomization.

If the test result is indeterminate, the investigator may repeat the test once or may proceed directly to perform workup for the test result as per local procedures. This action is at the discretion of the investigator. If the second test is negative, the patient may be randomized.

If the second test is positive or indeterminate, the investigator should perform workup as per local guidelines.

PPD skin test

PPD skin test will be performed as an alternative to Quantiferon in accordance with local guidelines and read at screening or within 6 months prior to randomization in order to evaluate an eventual infection with tuberculosis. The test dose is bioequivalent to 5 tuberculin units (or as according to local standard practice) of standard PPD injected intradermally into usually the volar surface of the forearm. The site is cleansed and the PPD extract is then injected into the most superficial dermal layer of the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

Because the reaction (induration) will take 48-72 hours to develop, the patient must return to the investigators' site within that time for a proper evaluation of the test site. This will determine whether the patient have had a significant reaction to the PPD test. A reaction is measured in millimeters of induration (hard swelling) at the site. A PPD skin induration ≥ 5 mm is interpreted as positive result.

Precautions against tuberculosis should be handled according to the best medical practice consistent to the local standards in each country with prior consultation with Novartis.

Patients requiring administration of antibiotics against latent tuberculosis should complete their treatment and should be considered cured prior to being re-considered for entry into this study (consultation with Novartis must occur before allowing the patient to enter the study).

Patients testing positive for latent TB per workup may be randomized to the trial if sufficient treatment has been completed according to local routine clinical practice. Patients testing positive for active TB per workup are not eligible for the study. Patients testing negative for TB (no signs of latent or active TB) per workup may be randomized to the trial.

6.2.3 pSS medical history and previous therapies

The date of first diagnosis of pSS will be collected from the patient's medical history. History of any other connective tissue disorders must be recorded on the Disease Diagnosis eCRF.

If the patient had previously received biologics for treatment of Sjögren's syndrome, the medications received must be recorded on the prior medications - pSS Specific Biologic Treatments eCRF. These may include infliximab, etanercept, rituximab, ocrelizumab, epratuzumab, belimumab, alefacept and abatacept. [redacted]

If the patient was previously treated with another disease modifying or immunosuppressive therapy for Sjögren's syndrome, these must be recorded on the 'Prior Medications – pSS

specific Non-biologic Treatment' eCRF. These treatments may include: hydroxychloroquine, methotrexate, azathioprine, mycophenolate, cyclophosphamide and chlorambucil.

6.2.4 Glandular biopsy result and other diagnostic assessments

Glandular tissue specimen of those patients [redacted] who have a biopsy taken during their participation in the study will be centrally biobanked and stored for later analysis by histologic and immunohistochemical methods.

Other mandatory assessments at screening and necessary for eligibility determination are listed below and described in the sections following below:

- ESSDAI value ≥6 at baseline, based on weighted scores of the biologic, hematologic, articular, cutaneous, glandular, lymphadenopathy and constitutional domains.
- ESSPRI value ≥5 at baseline
- [redacted]
- Stimulated whole salivary flow rate >0.1mL/min

Additionally, ESSDAI results will be used for stratification and must be entered into IRT at baseline.

6.3 Treatment exposure and compliance

All doses of study treatment administration will be recorded on the Dosage Administration Record eCRF page. Compliance to the planned administration schedule is expected to be high since the study treatment (s.c. administration of 2 injections) will be administered by trained study personnel. Compliance will also be assessed by means of site and patient-specific drug accountability by Novartis study personnel during the sitemonitoring visits using medication pack numbers, Drug Label Form information and information collected by IRT.

6.4 Efficacy

Clinical efficacy measurements related to primary and secondary objectives are outlined in the subsections below and include components of the ESSDAI and of the ESSPRI, SF-36, FACIT-F, Visual analog scale (VAS) of the PhGA of overall disease activity, and stimulated salivary flow assessments.

6.4.1 ESSDAI

The ESSDAI (Appendix 4) is a validated disease outcome measure for Sjögren's syndrome that will be applied to the study patients. The instrument contains 12 organ-specific domains contributing to disease activity. For each domain, features of disease activity are scored in 3 or 4 levels according to their severity. These scores are then summed across the 12 domains in a weighted manner to provide the total score.

6.4.2 Physician's global assessment of overall disease activity (PhGA)

PhGA will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question "Considering all the ways the disease affects your patient,

draw a line on the scale for how well his or her condition is today". Assessments will be done at baseline and every four weeks during period 2. To increase objectivity this assessment must be done prior to viewing the patient's global assessment of overall disease activity score.

[redacted]

6.4.3.1 ESSPRI

The ESSPRI is an established disease outcome measure for Sjögren's syndrome that will be applied to the study patients at screening, baseline and as per study assessment schedule (Table 6-1 and Table 6-2).

6.4.3.2 FACIT-F

The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F v4) is a short, 13-item, easy-to-administer tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on a four point Likert scale (4 = not at all fatigued to 0 = very much fatigued) (Webster et al., 2003). It will be applied to the study patients at baseline and every four weeks during period 2, and over 28 weeks in period 3.

6.4.3.3 SF-36

The Short Form-36 Health Survey (SF-36 v2 acute) is a survey evaluating individual patients' health status which also monitors and compares patients' disease burden. The physical and mental component scores will be assessed over 24 weeks every four weeks in period 2, and over 28 weeks in period 3.

6.4.3.4 Patient's global assessment (PaGA)

The PaGA of disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question on how well the patient is doing with the disease considering all aspects affected by the disease.

6.4.4 Salivary flow assessment

Both the amount and composition of saliva has been shown to reflect the damage caused by the disease process of Sjögren's syndrome (Pijpe et al., 2006). Stimulated and unstimulated whole and/or glandular salivary fluid is obtained from patients at baseline, and again at post treatment time points. Patients are instructed not to eat, drink or smoke for 90 minutes before assessment of salivary flow. All assessments are performed at a fixed time of the day to minimize fluctuations related to the circadian rhythm of salivary flow and composition. The start time and end time of saliva collection will be recorded to calculate the salivary flow rate.

Unstimulated and stimulated salivary secretions are collected over 5 minutes.The following saliva collection method is recommended to be utilized following the manufacturers' instructions for the unstimulated salivary flow assessment:

Passive drool collected using a Saliva Collection Aids constructed of polypropylene (e.g., Salimetrics Part no. 5016.02)

The following saliva collection method is recommended to be utilized following the manufacturers' instructions for the stimulated salivary flow assessment:

Cotton swabs containing citric acid solution (2% st/vol). The same method of stimulated salivary flow rate determination should be used for an individual patient at each assessment time point.

Additional material may be used following appropriate procedures. For more details refer to the laboratory manual. Saliva collected under unstimulated conditions may also be used for the assessment of saliva composition, [redacted] related to the disease or to pathways involved in the disease based on literature, new published results, or new internal results. The start time and end time of saliva collection will be recorded to calculate the salivary flow rate.

6.4.5 Appropriateness of efficacy assessments

The ESSDAI and ESSPRI are established and validated disease outcome measures for Sjögren's syndrome. Other chosen PROs are not disease specific, but applied conventionally in other chronic diseases. Stimulated salivary flow assessment has been suggested to reflect the damage caused by the disease process of Sjögren's syndrome (Pijpe et al., 2006). The monthly assessment schedule coincides with dosing intervals and the 24-week treatment duration (period 2) is a conventional treatment period for randomized clinical trials in this indication.

6.5 Safety

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, gums and teeth, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed. The investigator should ask the patient for and pay attention to presence of signs and symptoms of infection. Criteria to withhold study drug administration if infection is present or suspected are specified in Section 5.6.

Information for all physical examinations must be included in the source documentation at the study site and will not be recorded in the CRF. Significant findings that are present prior to informed consent are included in the Relevant Medical History CRF. Significant findings observed after informed consent signature which meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event CRF.

6.5.2 Vital signs

Vital signs include blood pressure (BP), pulse measurements, and body temperature. After the patient has been sitting for 3 minutes with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using an automated validated device with an appropriately sized cuff.

Clinically notable vital signs are defined in Appendix 1.

6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected except semi-quantitative 'dipstick' evaluation [redacted]. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.1 Hematology

The hematology panel will include: hemoglobin, hematocrit, red blood cell count, white blood cell count including lymphocytes, monocytes, absolute neutrophil count (ANC), eosinophils, basophils and platelet count will be measured. Assessments will be done at scheduled visits shown in Table 6-1, Table 6-2 and Table 6-3.

6.5.4.2 Clinical chemistry

The chemistry panel will include: albumin, alkaline phosphatase, total and differentiated bilirubin, calcium, chloride, fasting total cholesterol, LDL-cholesterol, HDL-cholesterol, creatinine, creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), α-amylase, γ-glutamyltransferase (GGT), glucose, sodium, potassium, inorganic phosphorus, bicarbonate, total protein, lactate dehydrogenase (LDH), triglycerides, magnesium, blood urea nitrogen (BUN), and uric acid, total immunoglobulin, IgG and IgM, [redacted]. Estimated creatinine clearance will be calculated using the MDRD formula.

Assessments will be done at scheduled visits shown in Table 6-1, Table 6-2 and Table 6-3.

[redacted]

6.5.4.5 Urinalysis

A urine sample (approx. 30 mL) will be obtained midstream in order to avoid contamination with epithelial cells and sediments, and to allow proper assessments.

Semi-quantitative 'dipstick' evaluation of the urine for the following parameters will be performed locally: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood at visits shown in Table 6-1, Table 6-2 and Table 6-3.

If the dipstick result is positive for albumin, nitrite, leucocytes and/ or blood, the sample will be analyzed locally for culture and for microscopic analysis of white blood cells, red blood cells and casts.

[redacted]

6.5.5 Electrocardiogram (ECG)

ECG assessments as indicated in the study assessment schedule will be performed locally. ECGs must be recorded (after 10 minutes rest in the supine position to ensure a stable baseline). The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling, and then all other assessments The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs on non-heat-sensitive paper and a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site. Results must be entered into the eCRF.

Each ECG tracing must be labeled with study number, patient initials, patient number, date and time, and filed in the study site source documents. For any ECGs with patient safety concerns (e.g., severe arrhythmia, conduction abnormality of QTcF >500 ms), two additional ECGs must be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the sponsor before administration of study treatment.

Clinically significant abnormalities must be recorded on the relevant section of the 'Medical History/Current Medical Conditions' or 'AE' eCRF page as appropriate.

6.5.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

For all WOCBP, highly effective contraception is required and a serum pregnancy test is required at screening, baseline and at monthly intervals during treatment (at scheduled visits). A serum pregnancy test will also be performed at the end of the study. Monthly urine tests must be done at home during months without study visits in period 4 until 1 year after last dose of study drug or study completion whichever occurs earlier.

6.5.7 Tolerability (systemic and local injection reactions)

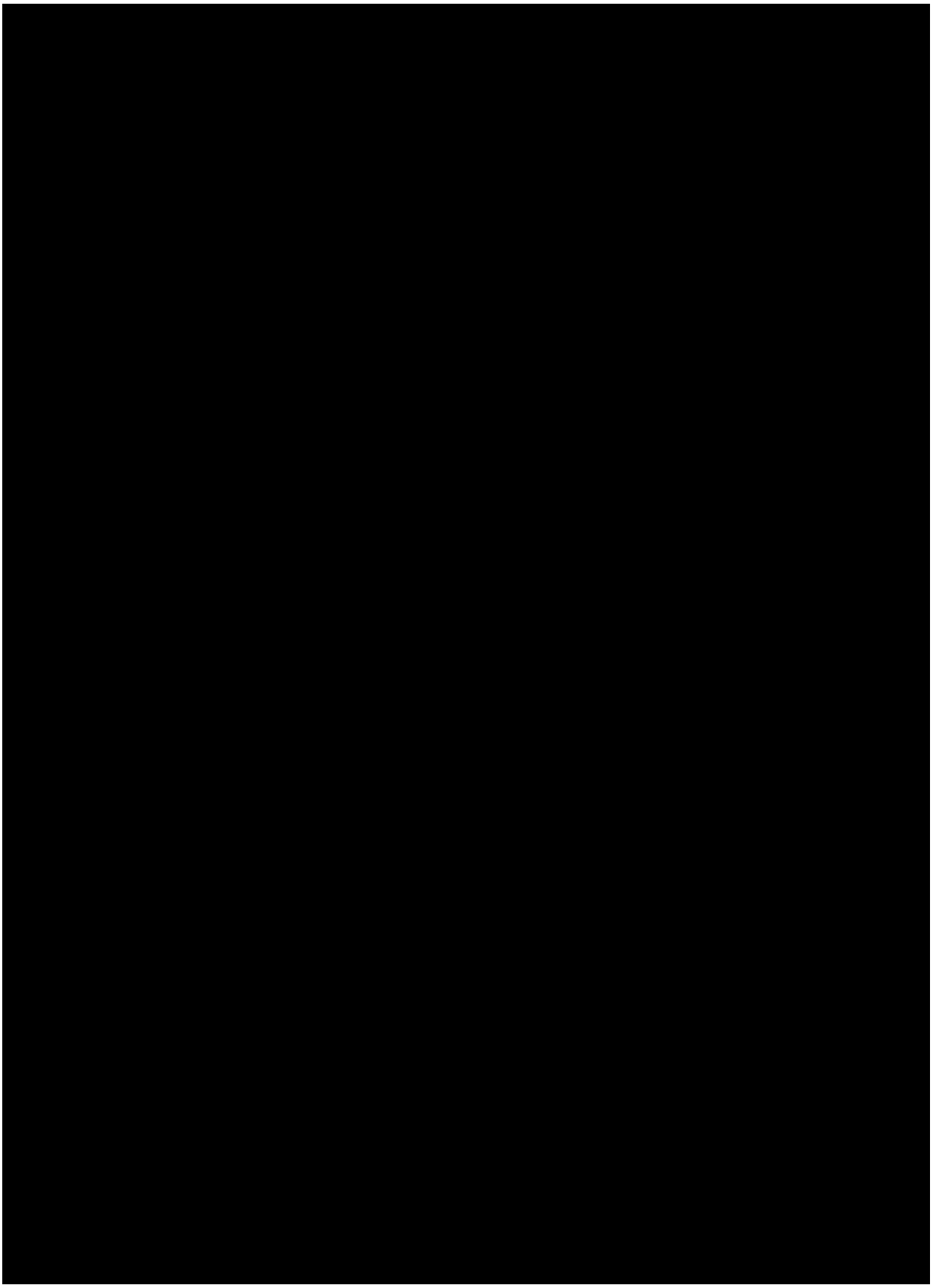
All occurrences of local site injection reactions as well as systemic injection reactions, self-reported or observed during clinic visits, must be recorded by the investigator. Any adverse events identified to be systemic injection reactions will be entered on the 'Systemic Injection Reaction for Study Treatment' eCRF and all adverse events identified to be local site injection reactions on the 'Injection Site Reaction for Study Treatment' eCRF.

6.5.8 Appropriateness of safety measurements

The safety assessments selected are standard for this indication and patient population. [redacted]

6.6 Other assessments

[redacted]



6.6.4 Resource utilization

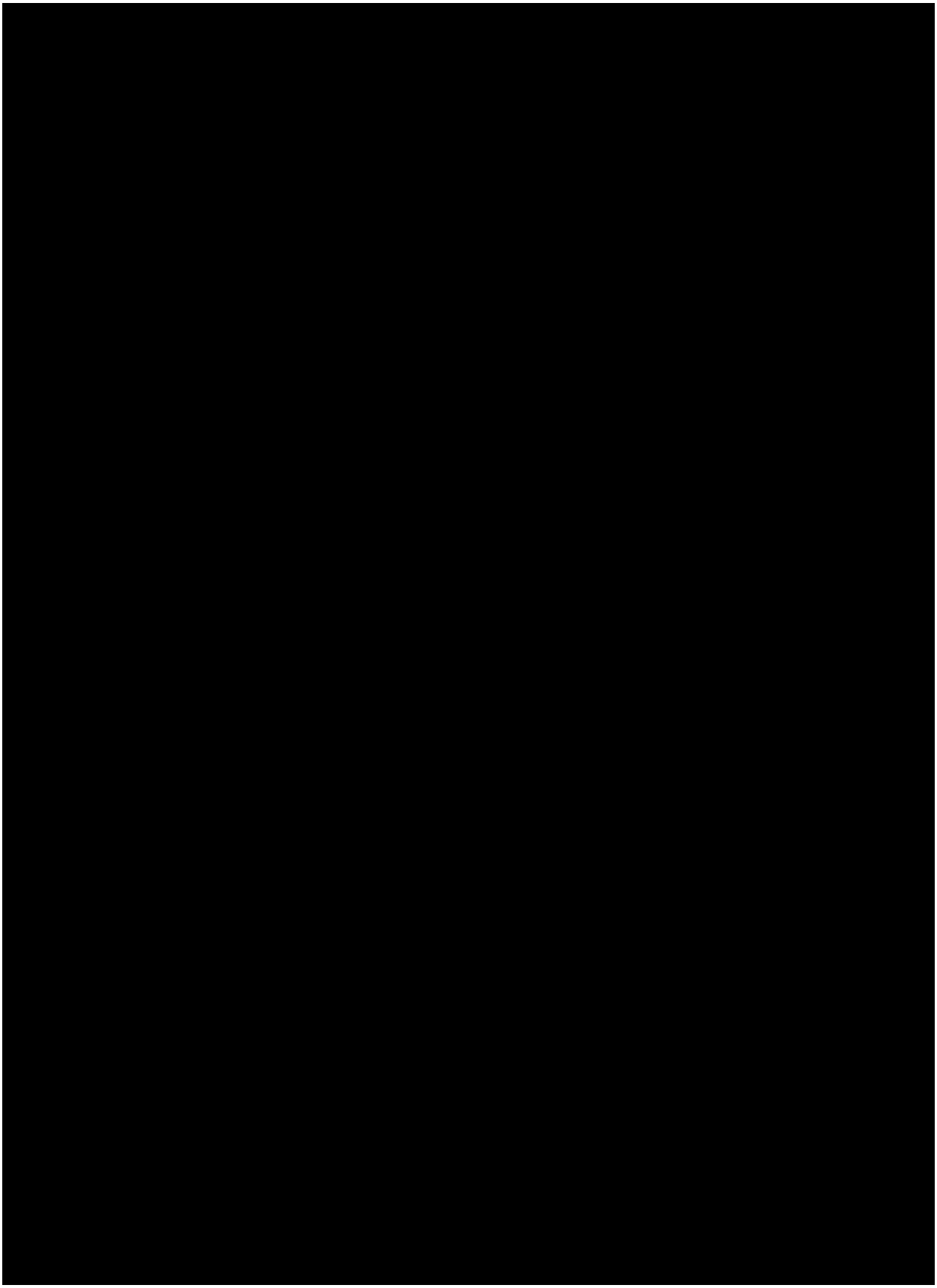
Not applicable.

6.6.5 Pharmacokinetics

At each visit indicated, a blood sample will be taken prior to dosing by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Further details on sample collection, numbering, processing and shipment can be found in the Laboratory Manual.

For all patients who entered period 3, an additional sample will be taken 72 hours post last dose of study treatment received (72 hours after week 48 dosing). This sample will be used to assess peak concentrations. All patients entering period 3 must return to the site for sample collection.

The detailed method description to assess VAY736 concentrations will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report (BDR).



7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade as follows:
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities

  - severe: prevents normal activities
  - its relationship to the study treatment:
  - "No Relationship to investigational treatment or other study treatment (pre-medication)" or
  - "Relationship to investigational treatment" or
  - "Relationship to other study treatment (pre-medication)" or
  - "Relationship to both investigational treatment and other study treatment or indistinguishable"
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding investigational treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g., further observation only)
- investigational treatment dosage increased/reduced
- investigational treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g., defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day

period after the last study visit should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each component of study treatment (VAY736/placebo or methylprednisolone premedication) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 14-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 14-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 14-2 in Appendix 2.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed must be recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.4 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum event:
  - confirmed (after ≥24h) increase in serum creatinine of ≥25% compared to baseline during normal hydration status
- Urine event
  - new onset (≥1+) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
  - new onset (≥1+), hematuria or glycosuria

Every renal laboratory trigger or renal event as defined in Table 15-1 in Appendix 3 should be followed up by the investigator or designated personnel at the trial site as summarized.

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

7.6 Pregnancy reporting

When pregnancy occurs in a patient in the study, the study drug must be discontinued, though the patient is encouraged to stay in the study and follow the assessments, if she agrees to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments. Unless the patient is in period 4 safety follow up period, all pregnancy cases have to be unblinded and the treatment communicated to investigator with the request to inform the patient which treatment she was on. This applies also when pregnancy occurs in partners of male patients.

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

7.7 Prospective suicidality assessment

Not applicable.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff [or CRO working on behalf of Novartis] review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Diary data will be entered into a paper diary by the patient and patients will fill in their PRO data (such as ESSPRI, FACIT-F, SF-36, [redacted] PaGA) in a site-based electronic device (e.g., tablet). The ESSDAI and PhGA will be collected on the site-based tablet by the investigator. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee (DMC)

An independent DMC will review cumulative, unblinded safety data continuously and at scheduled quarterly meetings. Of note, the clinical safety plan for this study includes close monitoring by the investigator for signs of infection and of hematologic parameters that include

neutrophil counts, and neutrophil parameters are included in the study entry criteria and stopping rules.

All SAEs reports will be transmitted to the DMC for review on a case by case basis. The collection and summary of these data will be prepared by a designated CRO or Novartis.

The DMC chair will inform the study team whether or not there is a safety concern after reviewing all the information received to date. Decisions based on the recommendations of the DMC will take into account the potential risks and benefits associated with continuing the enrollment of patients in the study or continued randomization into all dosing arms. Such information and recommendations will be used in the best interest of patients enrolled in the trial.

Details on the organization and function of the DMC will be described in the DMC charter.

8.5 Adjudication Committee

Not required.

9 Data analysis

The analyses will be conducted on all patient data at the time the trial ends and at the time when any interim analyses are performed. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Summary statistics for discrete variables will be presented in the number and percent of patients in each category.

If not otherwise specified, p-values will be presented as two-sided p-values and two-sided confidence intervals will be displayed.

The default level of significance will be set to 5% (two-sided, family-wise type-I-error).

The baseline value is defined as the last assessment prior to first dose administration. In case the scheduled baseline assessment value is missing the screening value will be used instead.

9.1 Analysis sets

The following analysis sets will be used in this trial:

Randomized set (RAN): All patients randomized are included in the Randomized Set. Patients will be analyzed according to the treatment assigned to at randomization. Unless otherwise specified, mis-randomized patients (randomized by mistake in IRT) will be excluded from the randomized set. The RAN will be used for summaries of patient disposition and analysis sets.

Mis-randomized patients are defined as those patients who were mistakenly randomized into the IVR prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized patients are treated as screen failures.

Full analysis set (FAS): comprises all patients in the RAN to whom study treatment has been assigned. Following the intent-to-treat principle, patients will be analyzed according to the

treatment assigned to at randomization and the stratum at baseline. FAS will be used for all efficacy variables, unless otherwise stated.

Safety set (SS): includes all patients who received at least one dose of study medication. Patient will be analyzed according to treatment received and the stratum at baseline. The safety set will be used in the analysis of all safety variables.

9.2 Patient demographics and other baseline characteristics

The analyses described in this section will be based on the randomized set and presented by the treatment groups randomized to at baseline.

Demographics and baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristic variables for each treatment group and for all patients in the randomized set. The number and percentage of patients in each category will be presented for categorical variables for each treatment group and all patients.

The following demographic variables and baseline disease characteristics will be summarized by treatment group:

- Gender, age, race, ethnicity, weight, height, BMI, disease duration and smoking status.
- ESSDAI and number of patients per ESSDAI stratum, ESSPRI, PhGA, PaGA, stimulated and unstimulated salivary flow, [redacted], use of DMARDs (split by type), B-cell count, [redacted], percentage of patients with history of prior biologics treatment use, and percentage of patients of confirmed positive glandular biopsy results.

Medical history

Any significant prior or active medical condition at the time of signing informed consent will be coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term.

9.3 Treatments

Study treatment

The analysis of study treatment data will be based on the safety set.

The duration (days) of study medication administration will be summarized. This will be calculated by subtracting the date of the first administration of study medication from the date of last administration and then adding the dosing interval for 28 days. In calculating the duration of treatment, days of temporary interruption of study medication for any reason will be included. Number and percentage of patients being exposed for prespecified time intervals (any, ≤3 months, ≤6 months, etc. up to ≤12 months) as well as cumulative exposure will also be summarized.

Prior and concomitant medication

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre-baseline and continued into the period where study treatment is administered.

Prior and concomitant medications will be summarized in separate tables for SAF. Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of patients receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

The number and percentage of patients receiving systemic therapies for pSS as prior and concomitant background medication will be presented separately by preferred term.

9.4 Analysis of the primary variable(s)

The purpose of this study is to characterize the dose response relationship among VAY736 doses (5, 50, 300 mg s.c. every 4 weeks) and placebo with regards to the change from baseline in ESSDAI at week 24 using all ESSDAI data collected during the 24 weeks of treatment during period 2. The goals of the study are:

- to confirm an overall dose-response signal, and
- to estimate the optimum dose that corresponds to the clinically relevant effect (i.e., 3-point change in ESSDAI) over placebo.

The generalized MCP-Mod methodology (Bretz et al., 2005; Pinheiro et al., 2014) will be used to address these goals. Testing will be done at one-sided 5% alpha level.

9.4.1 Variable(s)

The primary variable is the change from baseline in ESSDAI (12-domain score) over 24 weeks. This will be defined as the baseline ESSDAI minus the post-baseline ESSDAI value thus positive values will indicate improvement in disease status. The time point of primary interest is week 24 at which the dose-response will be evaluated.

The primary analysis will be based on the FAS.

9.4.2 Statistical model, hypothesis, and method of analysis

9.4.2.1 Repeated measures analysis

As a first step in the dose-response characterization a repeated measures model will be fitted to the changes from baseline in ESSDAI up to week 24. The change from baseline in ESSDAI is assumed to be normally distributed.

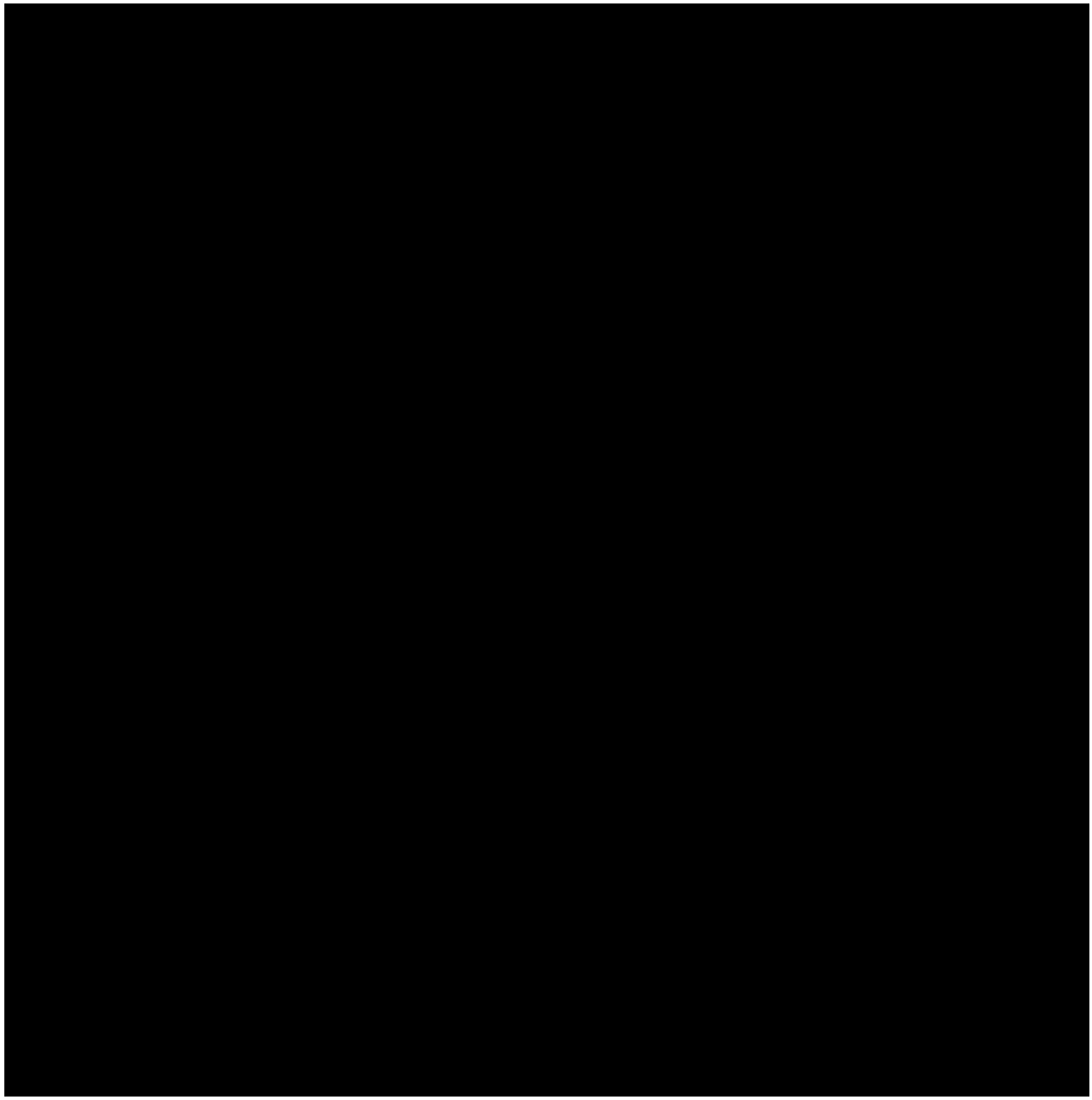
An MMRM model will be fitted to the changes from baseline in ESSDAI including all time points until week 24 including the following fixed factors

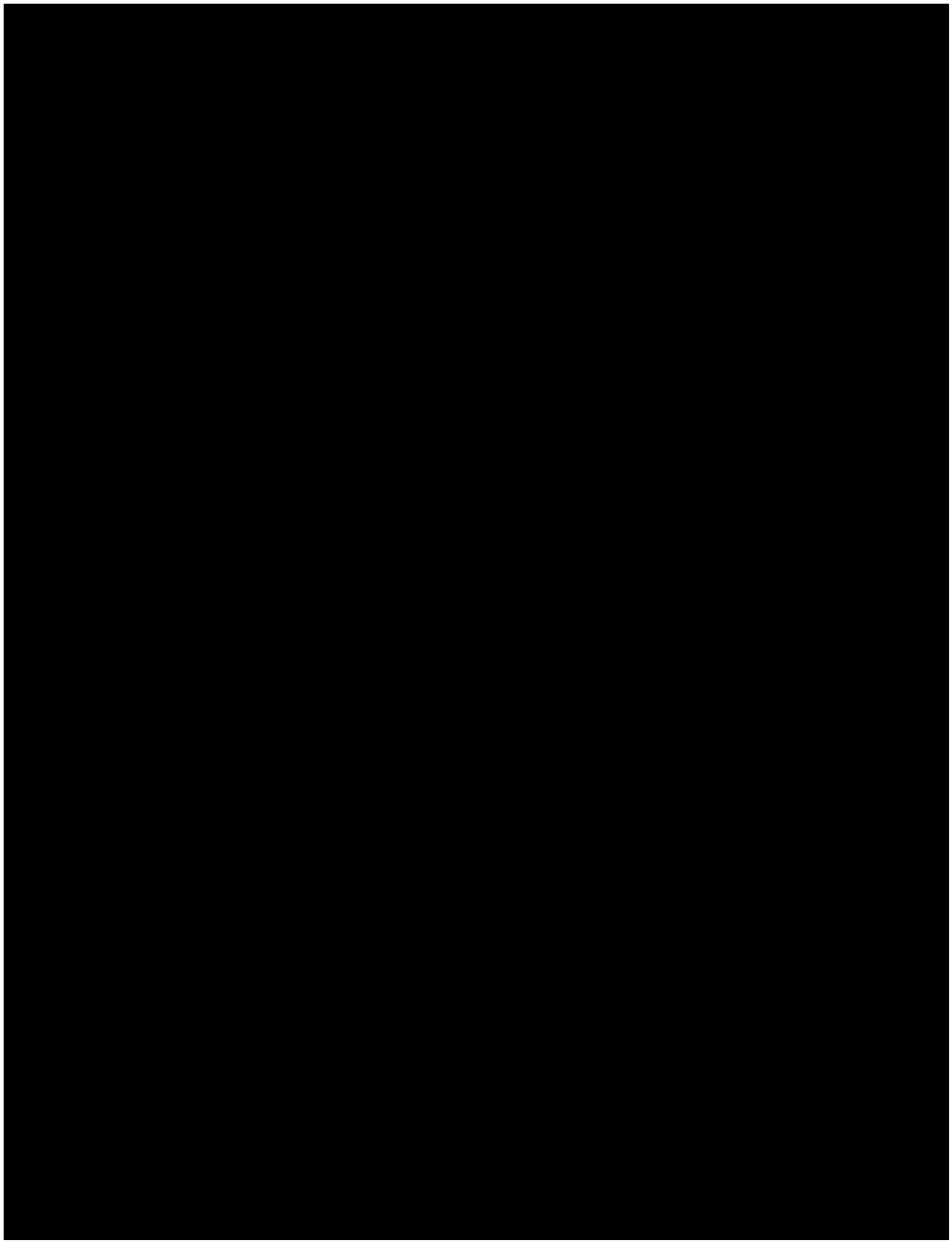
- treatment group

- visit
- treatment group by visit interaction
- stratification factor baseline ESSDAI score <10 or ≥10
- geographic region

as well as baseline ESSDAI as a continuous covariate. An unstructured variance-covariance matrix will be fitted to model the dependency between repeated observations. Graphical checks on the model assumptions of normality of the data will be provided.

The mean treatment effects will be estimated at week 24. Together with the estimated covariance matrix of these mean treatment effects they will be used in the dose-response modeling as described below.





[redacted]

9.4.3 Handling of missing values/censoring/discontinuations

For time points with missing data in one of the domains of the ESSDAI the total ESSDAI score will be set to missing. Alternative approaches of imputing these missing values might be considered.

Patients with missing data at one or more post-dose time points post baseline will be included in the analysis. If the baseline ESSDAI value is missing (and there is no the screening value available to replace it) the patient will be excluded from the primary analysis of change from baseline in ESSDAI.

The planned primary repeated measures mixed effects model assumes that missing values are missing at random. The reasonableness of this assumption will be checked during the blinded review of the data and if necessary further methods may be applied.

Sensitivity analyses of imputing might be considered to test the robustness of the results to the missing data assumptions. The following approaches could be explored:

- impute data based on the placebo treatment group data;
- impute data based on patients' data who discontinued treatment but continued study visits in case a sufficiently high number of such cases is observed.

9.4.4 Sensitivity analyses

To assess the potential influence of adherence to study procedures on the results of the primary analysis in the subset of patients more compliant with protocol requirements the following sensitivity analysis will be conducted: The full dose response modeling analysis as described in Section 9.4.2 will be repeated only including data of patients who have no protocol deviations that are expected to potentially confound the interpretation of primary analysis. These major protocol deviations will be identified from those included in the validation analysis plan prior to database lock and the unblinding of the study.

9.5 Analysis of secondary variables

For the secondary analyses missing data will not be imputed. If missing data occurs in a domain the corresponding total measurement will be set to missing. If a baseline assessment is missing (and there is no the screening value available to replace it) the corresponding change from baseline value will be missing.

9.5.1 Efficacy variables

The following variables will be analyzed using a similar MMRM model as in the primary analysis:

- Change from baseline in ESSPRI, FACIT-F, SF-36 (PCS and MCS), PhGA, PaGA and salivary flow rate (unstimulated and stimulated) over 24 weeks

The MMRM model is fitted to the respective variables changes from baseline including the time points specified above and will include the following explanatory variables:

- treatment group
- visit
- treatment group by visit interaction
- baseline value of variable analyzed,
- stratification factor baseline ESSDAI score <10 or ≥10
- geographic region.

The estimated means per dose and visit will be derived together with the 2-sided 95% confidence intervals. No hypothesis testing will be done.

For all parameters, summary statistics and listings together with graphical presentations of the original values and the changes from baseline will be presented by visit..

9.5.2 Safety variables

All safety variables will be analyzed on based on the safety set.

The number (and percentage) of patients with treatment emergent adverse events (events started after the first dose of investigational drug or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class (SOC) and preferred term (PT).
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

As appropriate, the incidence of AEs will be presented per 100 patient years of exposure.

A graphical display of relative frequencies within system organ classes and relative risks, as appropriate, will be presented.

Injection reactions

Injection reactions will be summarized by type of injection reaction (overall, local and systemic), by grading, and by visit.

Laboratory data

The summary of laboratory evaluations will be presented for [redacted] of laboratory tests [redacted].
Descriptive summary statistics for the change from baseline to each study visit will be presented by test group, and laboratory test .

Shift tables based on the normal laboratory ranges will also be provided. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. These summaries will be presented by laboratory test category.

The number and percentage of patients with clinically notable laboratory results after baseline will be presented.

Immunogenicity

All the results for immunogenicity data (anti-VAY736 antibodies) will be listed by visit/time.

If appropriate, summary statistics and shift tables will also be presented.

Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign.

ECG

Summary statistics will be presented for ECG variables by visit. Qualitative changes will be summarized.

9.5.3 Resource utilization

Not applicable.

9.5.4 Pharmacokinetics

PK data will be analyzed based on the SAF.

[redacted]

[redacted]

9.7 Interim analyses

An interim analysis may be performed at the discretion of the Sponsor or DMC prior to the primary efficacy analysis or the final analysis.

Interim analysis

An interim analysis will be performed prior to the primary efficacy analysis in addition to regularly scheduled safety reviews of data performed by the DMC. The purpose for this interim analysis may include any of the following features: 1) Stopping dose(s) for futility, 2) Blinded sample size re-assessment, 3) Determination that sufficient evidence exists based on the evaluation of the dose-response models evalutated, to accelerate Phase III planning activities prior to the primary efficacy analysis being performed.

This interim analysis will occur when at least 100 of the randomized patients (~55% and ~25 per treatment group) will have reached the primary endpoint at week 24.

Further details of the interim analysis will be provided in the DMC charter.

Primary efficacy analysis after all patients finished week 24

The primary efficacy analysis will be conducted when all randomized patients have finished period 2 (24 weeks of treatment). At this point the primary efficacy analysis and key secondary analyses will be conducted to allow planning activities for upcoming studies.

Analysis week 52

This analysis will occur when all patients complete Week 52 visit (treatment period 3) for the purpose of compiling a Clinical Study Report, prior to the final analysis.

For interim analysis the unblinded interim analysis results will be reviewed by an Interim Analysis Team. The Interim Analysis Team is a sub-team of the Clinical Trial Team. The Interim Analysis Team may communicate interim results (e.g., dose-response results or information needed for planning/modifying another study) to relevant Novartis teams. No further dissemination of interim results should occur, in particular not with individuals involved in treating the study‘s subjects or assessing clinical data (e.g., ECGs, symptoms) obtained in the study.

After the analysis week 52, all members of Novartis Clinical Trial Team may be unblinded.

10 Ethical considerations

10.1 Regulatory and ethical

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient’s representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved

in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

12 References (available upon request)

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[redacted]

13 Appendix 1: Clinically notable laboratory values and vital signs

Biochemistry

1. ALT (SGPT): ≥3xULN[1]
2. AST (SGOT): ≥3xULN[1]
3. Elevation of AST and/ or ALT (>3xULN) accompanied by elevated bilirubin (>1.5xULN, >2xULN)[1]
4. Any elevations of bilirubin; elevated total bilirubin (TBL) to >2x ULN[1]
5. Any elevations of ALP >1.5x ULN[1]
6. Gamma-Glutamyltransferase (GGT): >3x ULN
7. Creatinine (serum): ≥3x ULN
8. Creatinine clearance (CrCl) (Cockroft-Gault formula)[2]: ≥25% decrease from baseline
9. Triglycerides: >5x ULN
10. IgG and IgM: <LLN for 12 weeks

Hematology

1. Hemoglobin: ≥20 g/L decrease from baseline or <100 g/L
2. Platelet count[3]
   a. CTC Grade 1: <Lower Limit of Normal (LLN) – 75 x 10^9/L
   b. CTC Grade 2: <75 – 50 x 10^9/L
   c. CTC Grade 3: <50 – 25 x 10^9/L
   d. CTC Grade 4: <25x 10^9/L
3. White blood cell count[3]
   a. CTC Grade 1: <LLN – 3 x 10^9/L
   b. CTC Grade 2: <3 – 2 x 10^9/L
   c. CTC Grade 3: <2 – 1 x 10^9/L
   d. CTC Grade 4: <1 x 10^9/L
4. Absolute neutrophils[3]
   a. CTC Grade 1: <LLN – 1.5 x 10^9/L
   b. CTC Grade 2: <1.5 – 1 x 10^9/L
   c. CTC Grade 3: <1 – 0.5 x 10^9/L
   d. CTC Grade 4: <0.5 x $10E^9$/L
5. Absolute lymphocytes: <LLN
6. Absolute eosinophils: ≥2.5x, ≥3x ULN

Urinalysis

a. Protein urine dipstick: ≥++

Notable vital signs abnormalities in adult patients (≥18 years of age)

Post-baseline vital signs will be flagged as notable abnormalities as follows:

1. Systolic/Diastolic blood pressure: ≥25% decrease or ≥25 % increase from baseline

2. Pulse: ≥110 bpm with ≥15% change from baseline, or <50 bpm with ≥15% change from baseline

[1] Adapted from FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009)

[2] Cockroft-Gault formula (Men): CrCl (mL/min) = [((140-age (years)) x weight (kg)) / (serum creatinine (µmol/L) / 88.4) (mg/dL) x 72]

[2] Cockroft-Gault formula (Women): CrCl (mL/min) = [((140-age (years)) x weight (kg)) / (serum creatinine (µmol/L) / 88.4) (mg/dL) x 72] x 0.85

[3] Common Terminology Criteria for Adverse Events, US Department of Health and Human Services (v4.03: 14-Jun-2010)

14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤5 x ULN • 1.5 x ULN < TBL ≤2 x ULN
LIVER EVENTS	• ALT or AST >5 × ULN • ALP >2 × ULN (in the absence of known bone pathology) • TBL >2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST >3 × ULN and INR >1.5 • Potential Hy's Law cases (defined as ALT or AST >3 × ULN and TBL >2 × ULN [mainly conjugated fraction] without notable increase in ALP to >2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST >3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Table 14-2 Follow-up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
>8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
>3 × ULN and INR >1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
>5 to ≤8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
>3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
>3 to ≤5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
>2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
>2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
>1.5 to ≤2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST >3 × ULN and TBL >2 × ULN but without notable increase in ALP to >2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

15 Appendix 3: Specific renal alert criteria and actions

Table 15-1 Specific renal alert criteria and actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol; Protein-creatinine ratio (PCR) ≥150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.	

16 Appendix 4: ESSDAI questionnaire

Domain [weight]	Activity level	Description
Constitutional [3] Exclusion of fever of infectious origin and voluntary weight loss	No = 0	Absence of the following symptoms
	Low = 1	Mild or intermittent fever (37.5–38.5°C)/night sweats and/or involuntary weight loss of 5-10% of body weight
	Moderate = 2	Severe fever (>38.5°C)/night sweats and/or involuntary weight loss of >10% of body weight
Lymphadenopathy [4] Exclusion of infection	No = 0	Absence of the following features
	Low = 1	Lymphadenopathy ≥1 cm in any nodal region or ≥2 cm in inguinal region
	Moderate = 2	Lymphadenopathy ≥2 cm in any nodal region or ≥3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging)
	High = 3	Current malignant B-cell proliferative disorder
Glandular [2] Exclusion of stone or infection	No = 0	Absence of glandular swelling
	Low =1	Small glandular swelling with enlarged parotid (≤3 cm), or limited submandibular or lachrymal swelling
	Moderate = 2	Major glandular swelling with enlarged parotid (>3 cm), or important submandibular or lachrymal swelling
Articular [2] Exclusion of osteoarthritis	No = 0	Absence of currently active articular involvement
	Low = 1	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min)
	Moderate = 2	1–5 (of 28 total count) synovitis
	High = 3	≥6 (of 28 total count) synovitis
Cutaneous [3] Rate as 'no activity' stable long-lasting features related to damage	No = 0	Absence of currently active cutaneous involvement
	Low = 1	Erythema multiforma
	Moderate = 2	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute lutaneous lupus
	High = 3	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis
Pulmonary* [5] Rate as 'no activity' stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use, etc)	No = 0	Absence of currently active pulmonary involvement
	Low = 1	Persistent cough or bronchial involvement with no radiographic abnormalities on radiography or radiological or HRCT evidence of interstitial lung disease with no breathlessness and normal lung function test
	Moderate = 2	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NYHA II) or abnormal lung function tests restricted to 70%>DL_{CO}≥40% or 80%>FVC≥60%
	High = 3	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III, IV) or with abnormal lung function tests DL_{CO}<40% or FVC<60%
Renal [5] Rate as 'no activity' stable long-lasting features related to damage and renal involvement not related to the disease. If biopsy has been performed, please rate activity based	No = 0	Absence of currently active renal involvement with proteinuria <0.5 g/day, no haematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage
	Low = 1	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without haematuria or renal failure (GFR ≥60 ml/min)
	Moderate = 2	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 ml/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without haematuria or renal failure (GFR ≥60 ml/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate

Domain [weight]	Activity level	Description
on histological features first	High = 3	Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/day or haematuria or renal failure (GFR <60 ml/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinaemia-related renal involvement
Muscular* [6]	No = 0	Absence of currently active muscular involvement
Exclusion of weakness due to corticosteroids	Low = 1	Mild active myositis shown by abnormal EMG or biopsy with no weakness and creatine kinase (N<CK≤2N)
	Moderate = 2	Moderately active myositis confirmed by abnormal EMG or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N<CK≤4N)
	High = 3	Highly active myositis shown by abnormal EMG or biopsy with weakness (defi cit ≤3/5) or elevated creatine kinase (>4N)
PNS* [5]	No = 0	Absence of currently active PNS involvement
Rate as 'no activity' stable long-lasting features related to damage or PNS involvement not related to the disease	Low = 1	Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia.
	Moderate = 2	Moderately active peripheral nervous system involvement shown by NCS, such as axonal sensorimotor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinamic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia) Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia).
	High = 3	Highly active PNS involvement shown by NCS, such as axonal sensorimotor neuropathy with motor deficit ≤3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤3/5 or severe ataxia
CNS* [5]	No = 0	Absence of currently active CNS involvement.
Rate as 'no activity' stable long-lasting features related to damage or CNS involvement not related to the disease	Moderate = 2	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple schlerosis-like syndrome with symptoms restricted to pure sensory impairment or confirmed cognitive impairment.
	High = 3	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischaemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit.
Haematological [2]	No = 0	Absence of auto-immune cytopenia
For anaemia, neutropenia, and thrombopenia, only autoimmune cytopenia must be considered Exclusion of vitamin or iron deficiency, drug-induced cytopenia	Low = 1	Cytopenia of auto-immune origin with neutropenia (1000<neutrophils<1500/mm3), and/or anaemia (10<haemoglobin<12 g/dl), and/or thrombocytopenia (100000<platelets<150000/mm3) or lymphopenia (500<lymphocytes<1000/mm3).
	Moderate = 2	Cytopenia of auto-immune origin with neutropenia (500≤neutrophils≤1000/mm3), and/or anaemia (8≤haemoglobin≤10 g/dl), and/or thrombocytopenia (50000≤platelets≤100000/mm3) Or lymphopenia (≤500/mm3)
	High = 3	Cytopenia of auto-immune origin with neutropenia (neutrophils <500/mm3), and/or or anaemia (haemoglobin <8 g/dl) and/or thrombocytopenia (platelets <50000/mm3)

Domain [weight]	Activity level	Description
Biological [1]	No = 0	Absence of any of the following biological features
	Low = 1	Clonal component and/or hypocomplementaemia (low C4 or C3 or CH50) and/or hypergammaglobulinaemia or high IgG level between 16 and 20 g/L
	Moderate = 2	Presence of cryoglobulinaemia and/or hypergammaglobulinaemia or high IgG level >20 g/L, and/or recent onset hypogammaglobulinaemia or recent decrease of IgG level (<5 g/L)

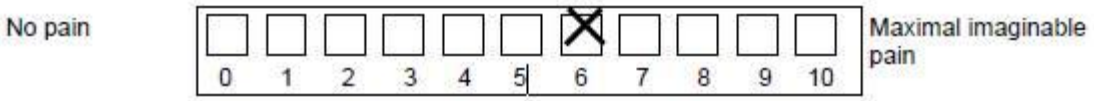
17 Appendix 5: ESSPRI

Your physician has asked you to answer several questions relating to your disease. To answer to these questions, please take into account how bad your symptoms have been at their worst during the last **two weeks** only.

Please **tick one box only** that best reflects your response.

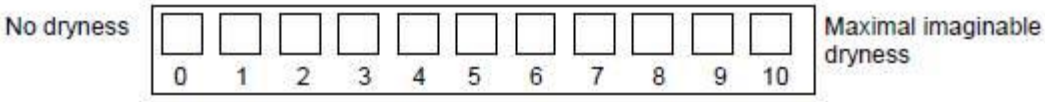
Please take care to answer **all the questions**.

Example:

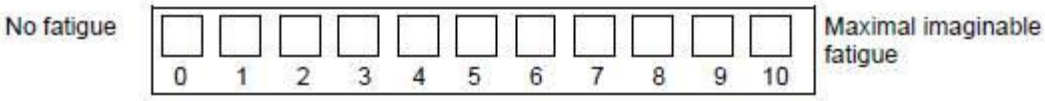


EVALUATION SCALES

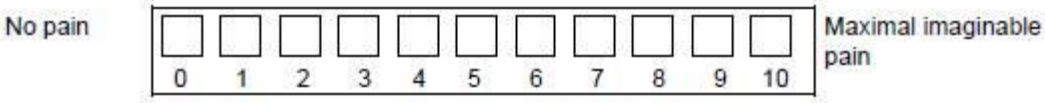
1. How severe has your **dryness** been during the last 2 weeks?



2. How severe has your **fatigue** been during the last 2 weeks?



3. How severe has your **pain** (joint or muscular pains in your arms or legs) been during the last 2 weeks?



18 Appendix 6: Blood collection for PK, [redacted] and IG [redacted]

Table 18-1 Blood volume to be collected by sample and visit

Visit	Week	PK			[redacted]	IG		[redacted]	Pregnancy	[redacted]	Hematology	Chemistry	[redacted]	Approximate Total Volume blood per visit[3]
		VAY736				ADA								
		Dose Ref ID	Sample no.	mL		Sample no.	mL		mL		mL	mL		mL
1 (Screening)[4]									1		2	3.5		22.5
101 (Baseline)	W0	1	1	2		301	3		1		2	3.5		29.5 (+6)[5]
102	W4	2	2	2					1		2	3.5		10.5
103	W8	3	3	2					1		2	3.5		8.5
104	W12	4	4	2		302	3		1		2	3.5		24.5
105	W16	5	5	2					1		2	3.5		8.5
106	W20	6	6	2					1		2	3.5		8.5
199[6]	W24	6/7	7	2		303	3		1		2	3.5		29.5
202[7]	W28	8	8	2					1		2	3.5		15.5
203[7]	W32	9	9	2					1		2	3.5		8.5
204[7]	W36	10	10	2		304	3		1		2	3.5		29.5

Visit	Week	PK			[redacted]	IG		[redacted]	Pregnancy	[redacted]	Hematology	Chemistry	[redacted]	Approximate Total Volume blood per visit[3]
		VAY736				ADA								
		Dose Ref ID	Sample no.	mL		Sample no.	mL		mL		mL	mL		mL
205[7]	W40	11	11	2					1		2	3.5		8.5
206[7]	W44	12	12	2					1		2	3.5		8.5
207[7]	W48	13	13	2		305	3		1		2	3.5		18.5
208[7]	D339	13	14	2										2
299[7]	W52								1		2	3.5		17.5
301[6]	W56[8]	6/13	15	2							2	3.5		12.5
302[6]	W60[8]	6/13	16	2		306	3				2	3.5		17.5
303[6]	W64[8]	6/13	17	2							2	3.5		12.5
304[6]	W68[8]	6/13	18	2		307	3				2	3.5		15.5
305 and 306[6]	W76/84[8]	6/13	19/20	2							2	3.5		12.5
307/308/309[6]	W96/108/	6/13									2	3.5		10.5

Visit	Week	PK			[redacted]	IG		[redacted]	Pregnancy	[redacted]	Hematology	Chemistry	[redacted]	Approximate Total Volume blood per visit[3]
		VAY736				ADA								
		Dose Ref ID	Sample no.	mL		Sample no.	mL		mL		mL	mL		mL
	132[8]													
399	156[8]		21[9]	2		308	3				2	3.5		22.5
Unscheduled visits			1001 1002 …	2		1301, 1302, …	3				2	3.5		17.5

[redacted]

3. **The volumes are approximate and may change depending on specific central laboratory that may be contracted**
4. **Following samples at screening visit only: Viral serology: 3 mL; Quantiferon: 3 mL**

[redacted]

6. **Not applicable to patients not treated in period 3**
7. **Study week for patients treated in period 3. For patients who completed treatment in period 2 the vistis correspond to study weeks 28, 32, 36, 40, 48, 56, 68, 80 and 104 respectively, as per Table 6-3**
8. **Only for patients who prematurely withdrew**

19 Appendix 7: Hepatitis B serology

Table 19-1 Hepatitis B serology result, interpretation and patient eligibility

Test	Test result	Interpretation	Patient Eligibility
HBsAg Anti-HBc Anti-HBs	Negative Negative Negative	Susceptible	Patient eligible
HBsAg Anti-HBc Anti-HBs	Negative Positive Positive	Immune due to natural infection	Not eligible
HBsAg Anti-HBc Anti-HBs	Negative Negative Positive	Immune due to hepatitis B vaccination	Patient eligible
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Positive Negative	Acutely infected	Not eligible
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Negative Negative	Chronically infected	Not eligible
HBsAg Anti-HBc Anti-HBs	Negative Positive Negative	Interpretation unclear; four possibilities: 1.Resolved infection (most common) 2.False-positive anti-HBc, thus susceptible 3. “Low level” chronic infection 4. Resolving acute infection	Not eligible