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VAY736

Clinical Trial Protocol CVAY736X2203

# A randomized, partial-blind, placebo-controlled trial evaluating the efficacy, safety, pharmacokinetics and pharmacodynamics of VAY736 in the treatment of patients with pemphigus vulgaris

| | |
|---|---|
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## Notification of serious adverse events

A serious adverse event (SAE) is any event which is fatal or life-threatening, which requires or prolongs hospitalization, which is significantly or permanently disabling or incapacitating, which constitutes a congenital anomaly or a birth defect, or which is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

**Any SAE** occurring in a subject **from consent until 30 days after stopping the trial/study drug** must be reported either on the paper SAE report form or via the electronic SAE form within the clinical data capture system (where available).

For SAEs reported using the **paper SAE report form**, the investigator will ensure that the form is completed and **faxed** by the **investigator to the local Novartis Chief Medical Officer within 24 hours** of learning of the occurrence of the SAE even if the SAE does not appear to be drug-related**.** The original SAE form, together with the fax confirmation sheet, must be kept with the case report forms at the study site.

For SAEs recorded ***electronically*** in the Novartis clinical data capture system, information should be **entered, saved and e-signed within 24 hours of awareness of the SAE**. These data will automatically be submitted to Novartis Drug Safety and Epidemiology.

More details in **Section 7** of this protocol.

### Fax numbers of local Novartis Chief Medical Office and Patient Safety

| | |
|---|---|
| Austria | Fax (+ 43) 1 866 57 6458 |
| France | Fax (+ 33) 1 5547 67 00 |
| Germany | Fax (+ 49) 911 273 12 985 |
| | if first line busy: (+ 49) 911 273 12 703 |
| Israel | Fax (+ 972) 3 923 18 17 |
| Italy | Fax (+39) 02 967 03051 |
| Taiwan | Fax (+ 886) 2 23 22 41 92 |
| United Kingdom | Fax (+44) 845 6011418 |
| | If first line busy: (+44) 0276 698454 |
| United States of America | Fax (+ 1) 877 778 9739 |

In addition, the investigator will inform the following responsible person(s) of Novartis Translational Sciences:

Personal Protected Data

Any update to the Novartis CMO&PS or personnel information required during the course of the study will be communicated directly to the relevant Investigator site(s); a specific protocol amendment should not be required.

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## List of abbreviations

| | |
|---|---|
| ABSIS | Autoimmune Bullous Skin disease Intensity Score |
| ADA | anti-drug antibody |
| | Commercially Confidential Information |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine aminotransferase |
| ALP | alkaline phosphatase |
| ANCOVA | analysis of covariance |
| | Commercially Confidential Information |
| AST | aspartate aminotransferase |
| | Commercially Confidential Information |
| BMI | Body Mass Index |
| BP | blood pressure |
| BUN | blood urea nitrogen |
| CBC | complete blood count |
| CD-ROM | compact disc – read only memory |
| CFR | Code of Federal Regulation |
| CK | creatinine kinase |
| (e)CRF | (electronic) Case Report/Record Form |
| $CO_2$ | carbon dioxide |
| CRO | Contract Research Organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | coefficient of variation |
| DLT | Dose limiting toxicities (s) |
| DMC | Data Monitoring Committee |
| | Commercially Confidential Information |
| EC | Ethics committee |
| ECG | Electrocardiogram |
| EDC | Electronic Data Capture |
| ELISA | Enzyme-linked immunosorbent assay |

| | |
|---|---|
| EoS | End of Study |
| FACS | Fluorescence-activated cell sorting |
| Fc | Fragment crystallizable |
| FDA | Food and Drug Administration |
| FIH | First in Human |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| γ-GT | Gamma-glutamyl transferase |
| h | hour |
| hCG | human chorionic gonadotropin |
| HAs | Health Authorities |
| HIV | human immunodeficiency virus |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IGA | Investigator Global Assessment |
| IgG | immunoglobulin class G |
| i.v. | intravenous |
| IVIG | Intravenous Immunoglobulin |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| LDH | lactate dehydrogenase |
| LFT | Liver function test |

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| | |
|---|---|
| LON | late onset neutropenia |
| mAB | monoclonal antibody |
| mg | milligram(s) |
| mL | milliliter(s) |
| MMF | Mycophenolate mofetil |
| NSAIDs | Nonsteroidal Anti-Inflammatory Drugs |

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|---|---|
| PDAI | Pemphigus Disease Area Index |

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|---|---|
| PK | pharmacokinetic(s) |

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| | |
|---|---|
| PV | Pemphigus vulgaris |
| RA | Rheumatoid Arthritis |
| RAP | Reporting and Analysis Plan |
| RBC | red blood cell(s) |
| REB | Research Ethics Board |
| RF | rheumatoid factor |
| SAE | serious adverse event |
| s.c. | subcutaneous |
| SAD | single ascending dose |
| SD | standard deviation |
| SGOT | serum glutamic oxaloacetic transaminase |
| SGPT | serum glutamic pyruvic transaminase |
| SoC | standard of care |
| TBL | total bilirubin |
| TK | toxicokinetic(s) |
| TMDD | Target-mediated drug disposition |
| ULN | upper limit of normal |

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| | |
|---|---|
| WBC | white blood cell(s) |
| WOCBP | women of child-bearing potential |

## Pharmacokinetic definitions and symbols

| | |
|---|---|
| AUCinf | The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume] |
| AUClast | The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume] |
| Cmax | The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume] |
| T1/2 | The terminal elimination half-life [time] |
| Tmax | The time to reach the maximum concentration after drug administration [time] |

## Glossary of terms

| | |
|---|---|
| Assessment | A procedure used to generate data required by the study. |
| Enrollment | Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol). |
| Investigational drug | The study 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". |
| Investigational treatment | All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls.<br>This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination.<br>Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage. |
| Subject number | A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study. |
| Period | A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc. |
| Premature subject withdrawal | Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned. |
| Randomization number | A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment. |
| Study completion | Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later. |
| Study drug/treatment | Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy. |
| Study drug discontinuation | Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal. |

| | |
|---|---|
| Subject | An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient. |
| Variable | Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints. |

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## Protocol synopsis

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|---|---|
| **Protocol number** | CVAY736X2203 |
| **Title** | A randomized, partial-blind, placebo-controlled trial evaluating the efficacy, safety, pharmacokinetics and pharmacodynamics of VAY736 in the treatment of patients with pemphigus vulgaris |
| **Brief title** | Study of efficacy and safety of VAY736 in patients with Pemphigus vulgaris |
| **Sponsor and Clinical Phase** | Novartis<br>Phase II |
| **Investigation type** | Drug |
| **Study type** | Interventional |
| **Purpose and rationale** | To determine if a single intravenous dose of VAY736 can reduce disease activity in Pemphigus vulgaris. As determined by the change in Pemphigus Disease Area Index (PDAI) compared to placebo. The study will also provide safety and tolerability information for VAY736 in PV patients. |
| **Primary Objective(s) and Key Secondary Objective** | To compare the efficacy of a single i.v dose of VAY736 relative to placebo in reducing clinical disease activity of pemphigus vulgaris patients, as determined by the change in Pemphigus Disease Area Index (PDAI) between baseline and 12 weeks |
| **Secondary Objectives** | • To evaluate the safety and tolerability of VAY736 in patients with PV<br>• To evaluate the effect of VAY736 in PV patients as assessed by the Autoimmune Bullous Skin disease Intensity Score (ABSIS) at 12 weeks<br>• To evaluate the effect of VAY736 in PV patients as assessed by Investigator Global Assessment (IGA) at 12 weeks<br>• To evaluate VAY736 pharmacokinetics in serum in PV patients |
| **Study design** | This is a non-confirmatory, randomized, partial-blind, placebo-controlled trial evaluating the efficacy, safety, pharmacokinetics Commercially Confidential Information of VAY736 in the treatment of patients with pemphigus vulgaris.<br><br>Approximately 24 patients with mild-moderate active PV will be randomly assigned in a blinded fashion to one of three single dose treatment arms. Recruitment will be staggered and progression between doses is dependent upon a safety review milestone.<br><br>In the pre-safety review period, 9 patients will be randomized to a single dose of either 3 mg/kg VAY736 (6 patients) or placebo (3 patients). Once patients have achieved Week 6, a safety review will take place. If there are no safety signals, recruitment will restart into the 3 mg/kg (3 patients) and placebo (3 patients) arms and commence to the 10 mg/kg arm (9 patients). Following the single dose on Day 1, standard of care medications will be maintained at a stable level until 'disease control' in signs/symptoms of PV. The standard of care medication will then be tapered to safely deliver the patient to the lowest dose level required to maintain control of the disease.<br><br>Patients will enter into a double-blind follow up period for 24 weeks post dose, at which point their treatment will be unblinded. Patients that received VAY736 will then enter into a long-term follow up Commercially Confidential Information . Patients that received placebo will be offered open-label single dose IV VAY736 treatment. |

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| **Population** | The study population will be comprised of male and female Pemphigus vulgaris patients, aged between 20 and 70 years, inclusive.<br><br>It is planned that up to approximately 32 patients may be enrolled (randomized) into the study; at least 24 patients are expected to complete the study. |
| **Inclusion criteria** | **All patients**<br>• Diagnosis of PV according to (i) presence of blisters or erosions of the skin or mucous membranes, plus (ii) characteristic documented histological findings in the skin, plus (iii) characteristic findings from direct immunofluorescence in Commercially Confidential Information. If results are not available, biopsies and a blood sample have to be taken at screening to confirm diagnosis.<br>• Presence of mild to moderate active PV at Baseline as defined by a PDAI score between 20 and 60 (inclusive) or for a PDAI below 20: an IGA of 2 to 3 (e.g. at least 1% but not more than 10 % BSA involvement).<br>• On a stable dose(s) of oral corticosteroid +/- adjuvant therapy of azathioprine or mycophenolate mofetil. Requirements for these standard-of-care (SoC) medications are:<br>  • Oral corticosteroids alone, with steroid dose to be equivalent to prednisone ≥15 mg per day but no greater than 2 mg/kg/day; or<br>  • Oral corticosteroid + azathioprine, with steroid dose to be equivalent to prednisone ≥2.5 mg per day but no greater than 1 mg/kg/day, and azathioprine with no specific daily dose requirement; or<br>  • Oral corticosteroid + mycophenolate mofetil, with steroid dose to be equivalent to prednisone ≥2.5 mg per day but no greater than 1 mg/kg/day, and mycophenolate mofetil with no specific daily dose requirement.<br><br>SoC medications considered stable if the daily dose has not changed within the 7 days preceding the day of dosing (Day 1) for oral corticosteroid, or within the 14 days preceding the day of dosing (Day 1) for azathioprine and mycophenolate mofetil.<br><br>**Open-label patients (i.e. for placebo-treated patients)**<br>• Presence of mild to moderate active PV at unblinding, as defined by a PDAI score more than 10.<br>• On a stable dose(s) of oral corticosteroid +/- adjuvant therapy of azathioprine or mycophenolate mofetil. Requirements for these standard-of-care (SoC) medications are:<br>  • Oral corticosteroids alone, with steroid dose to be equivalent to prednisone ≥15 mg per day but no greater than 2 mg/kg/day; or<br>  • Oral corticosteroid + azathioprine, with steroid dose to be equivalent to prednisone ≥2.5 mg per day but no greater than 1 mg/kg/day, and azathioprine with no specific daily dose requirement; or<br>  • Oral corticosteroid + mycophenolate mofetil, with steroid dose to be equivalent to prednisone ≥2.5 mg per day but no |

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| | greater than 1 mg/kg/day, and mycophenolate mofetil with no specific daily dose requirement.<br>SoC medications considered stable if the daily dose has not changed within the 7 days preceding the day of dosing (Day 1) for oral corticosteroid, or within the 14 days preceding the day of dosing (Day 1) for azathioprine and mycophenolate mofetil. |
| **Exclusion criteria** | **All patients**<br>• Known hypersensitivity to any constituents of the study drug, to murine, chimeric or human antibodies, or to drugs of similar chemical classes (e.g., IgG1 biologics). Also, known hypersensitivity to study drug premedication (paracetamol or acetaminophen) and H1 receptor blocker).<br>• Prior use in the 12 months prior to Screening of any B-cell depleting therapy e.g., rituximab or other anti-CD20 mAb, anti-CD22 mAb, anti-CD52 mAb.<br>• Use of prednisone or other systemic steroids for conditions other than pemphigus vulgaris within the 1 month prior to Baseline.<br>• Use of topical steroids (or other topical treatment for PV) within 2 weeks prior to Baseline.<br>• Recent previous treatment with phototherapy, biological therapy, immunosupressive agents such as azathioprine (unless it is used as SoC medications for pemphigus treatment as per inclusion criteria # 5), dapsone, or methotrexate. The following washout period will be required for such patients to be eligible to participate in the trial:<br>• 6 months washout prior to Screening for IVIg, plasmapheresis, immunoadsorption or i.v. or oral cyclophosphamide;<br>• 3 months washout prior to Screening for etanercept, adalimumab, ustekinumab, infliximab or any other immunologically active biologic therapy;<br>• 1 month washout prior to Screening for UVB/PUVA therapy, dapsone, methotrexate, and any systemic immunosupressants or other systemic treatment for PV.<br>• Active viral, bacterial or other infections at the time of Screening or Baseline, or history of recurrent clinically significant infection or of recurrent bacterial infections with encapsulated organisms.<br>• Evidence of active or latent tuberculosis (TB), or inadequately treated infection with TB<br>Decisions about management of previous treatments are left to the treating physician in line with the patients' choices, and should be conducted according to local standard of care best practice. The present protocol does not support stopping a medication if the sole purpose is to allow a patient to then become eligible to enter the study.<br>**Open-label patients (i.e. for placebo-treated patients)**<br>• CBC laboratory values as follows:<br>• Hemoglobin <10.0 g/dL<br>• White blood cell count <3,000/µL<br>• Platelets <100,000/µL<br>• Absolute neutrophil count ≤1,500/ µL |
| **Investigational and reference therapy** | VAY736 3 mg/kg; 10 mg/kg |

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| **Efficacy assessments** | • Pemphigus Disease Area Index<br>• Autoimmune Bullous Skin disease Intensity Score<br>• Investigator Global Assessment |
| **Safety assessments** | • Physical examination<br>• Vital signs<br>• 12-Lead ECG<br>• Hematology, Blood chemistry, Urinalysis<br>• Adverse Events/Serious Adverse Events<br>• Concomitant Medications<br>Commercially Confidential Information |
| **Other assessments** | • Pharmacokinetics<br>Commercially Confidential Information |
| **Data analysis** | The change from baseline in PDAI skin and mucous membranes activity score will be analyzed using a mixed effects model for repeated measures including terms for the patient effect (as a random effect), treatment effect (VAY736 3 mg/kg, VAY736 10 mg/kg or placebo), follow-up time points and the interaction between time and treatment (all as fixed effects) adjusting for the baseline PDAI skin and mucous membranes score as a covariate. This statistical analysis model will include change from baseline data on the PDAI from all post-baseline time points at which it was recorded (i.e. weeks 3, 6, 9, 12, 16, 20 and 24) but the primary comparison is made for week 12. The analysis model may be adjusted for increases in SoC, if appropriate.<br><br>A positive sign of therapeutic effects will be considered to be a difference of at least 10 points in the change from baseline between the 10 mg/kg dose of VAY736 and placebo with a moderate level of evidence (i.e. 50%). Additionally there should be a high level of evidence (i.e. 90%) for a difference between the 10 mg/kg dose of VAY736 and placebo. The estimates of the posteriors probabilities of these criteria being met will be provided for each VAY736 dose separately and for the combined 3 mg/kg and 10 mg/kg doses, assuming standard non-informative prior Normal distributions. In case there is no difference between treatments on the PDAI at week 12 but significantly higher increases of SoC in the placebo arm, this may also be considered a sign of efficacy.<br><br>Secondary efficacy variables (i.e. change from baseline to week 12 measurements of PDAI total score and ABSIS) will be analyzed following a similar approach. The number and percentage of patients experiencing control of disease activity will be presented for each visit. The posterior distributions of the difference in proportions between each dose of VAY736 and placebo, given the data, will be estimated assuming a "neutral", non-informative Beta (1/3, 1/3) prior for each treatment group.<br><br>The number and percentage of patients in each category of response for the IGA will be presented for each visit.<br>Commercially Confidential Information |

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| **Key words** | Pemphigus vulgaris, pemphigus, |

## Assessment schedule

| **Study Phase** | **Screening** | **Double-blind Period** | | | | | | | | | | **Long term Follow-up[19]** | | **End of study (EoS)** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Visit 1** | **Visit 2 Baseline/Dosing** | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6** | **Visit 7** | **Visit 8** | **Visit 9** | **Visit 10** | **Visit 11** | **Visit 12, 13 and 14** | **V515, V516** | **Visit 777** |
| **Weeks post-dose** | **-** | **0** | **1** | **2** | **3** | **6** | **9** | **12** | **16** | **20** | **24** | **32, 40, 52** | **76, 100** | |
| **Study day(s)** [1] | **-28 to -1** | **1** | **8** | **15** | **22** | **43** | **64** | **85** | **113** | **141** | **169** | **225, 281, 365,** | **532, 700** | |
| **Allowed time window** [1] | **-** | **± 2 h for 24 h** | **± 2d** | **± 2d** | **± 3d** | **± 4d** | **± 4d** | **± 4d** | **± 7d** | **± 7d** | **± 7d** | **± 2 weeks** | **± 2 weeks** | |
| Informed consent | X | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X[2] | | | | | | | | | | | | |
| Relevant medical history / current medical conditions | X | X[2] | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | |
| Pemphigus vulgaris (PV) history/ Previous PV treatment | X | | | | | | | | | | | | | |
| Confirmation of PV diagnosis (if required, local analysis)[3] | | | | | | | | | | | | | | |
| Biopsy of lesional skin for histologic confirmation of PV | X | | | | | | | | | | | | | |
| Biopsy of perilesional skin for direct immunofluorescence (DIF) | X | | | | | | | | | | | | | |
| Blood sample for western blot or ELISA | X | | | | | | | | | | | | | |
| Physical examination | X | X | X | X | | X | X | X | X | X | X | X | | X |
| Vital signs[4] and body temperature | X | X, 24 h | X | X | | X | X | X | X | X | X | X | | X |
| Body height | X | | | | | | | | | | | | | |
| Body weight | X | X[2] | | | | | | | | | X | | | X |
| 12-lead ECG | X | X[2] | X | X | | X | X | X | X | X | X | X | | X |

| Study Phase | Screening | Double-blind Period | | | | | | | | | | Long term Follow-up[19] | | End of study (EoS) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | Visit 1 | Visit 2 Baseline/Dosing | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Visit 8 | Visit 9 | Visit 10 | Visit 11 | Visits 12, 13 and 14 | V515, V516 | Visit 777 |
| Weeks post-dose | - | 0 | 1 | 2 | 3 | 6 | 9 | 12 | 16 | 20 | 24 | 32, 40, 52 | 76, 100 | |
| Study day(s) [1] | -28 to -1 | 1 | 8 | 15 | 22 | 43 | 64 | 85 | 113 | 141 | 169 | 225, 281, 365 | 532, 700 | |
| Allowed time window [1] | - | ± 2 h for 24 h | ± 2d | ± 2d | ± 3d | ± 4d | ± 4d | ± 4d | ± 7d | ± 7d | ± 7d | ± 2 weeks | | |
| Laboratory Safety Tests | | | | | | | | | | | | | | |
| Hematology incl. differential WBC count | X | X, 24 h | X | X | X | X | X | X | X | X | X | X | X | X |
| Clinical chemistry | X | X, 24 h | X | X | X | X | X | X | X | X | X | X | | X |
| Urinalysis | X | X, 24 h | X | X | X | X | X | X | X | X | X | X | | X |
| Ig subset and total | | | | | | | | | | | | | X | X |
| Hepatitis and HIV screen | X | | | | | | | | | | | | | |
| Alcohol test and Drug screen | X | | | | | | | | | | | | | |
| TB assessment | X | | | | | | | | | | | | | |
| Pregnancy (hCG) test[5] | X | X | | | X | X | X | X | X | X | X | X | | X |
| FSH[6] | X | | | | | | | | | | | | | |
| Premedication[7] | | X | | | | | | | | | | | | |
| Study Drug administration[7] | | X | | | | | | | | | | | | |
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| **Study Phase** | **Screening** | **Double-blind Period** | | | | | | | | | | **Long term Follow-up**[19] | | **End of study (EoS)** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Visit 1** | **Visit 2 Baseline/Dosing** | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6** | **Visit 7** | **Visit 8** | **Visit 9** | **Visit 10** | **Visit 11** | **Visits 12, 13 and 14** | **V515, V516** | **Visit 777** |
| **Weeks post-dose** | **-** | **0** | **1** | **2** | **3** | **6** | **9** | **12** | **16** | **20** | **24** | **32, 40, 52** | **76, 100** | |
| **Study day(s)** [1] | **-28 to -1** | **1** | **8** | **15** | **22** | **43** | **64** | **85** | **113** | **141** | **169** | **225, 281, 365** | **532, 700** | |
| **Allowed time window** [1] | **-** | **± 2 h for 24 h** | **± 2d** | **± 2d** | **± 3d** | **± 4d** | **± 4d** | **± 4d** | **± 7d** | **± 7d** | **± 7d** | **± 2 weeks** | | |
| Pharmacokinetic blood sampling | | X, 2, 24 h[12] | X | X | X | X | X | X | X | X | X | | | X[21] |
| Standardized Body Photographs | | X | | | X | X | X | X | X | X | X | X | | X |
| Pemphigus Disease Area Index (PDAI)[13] | X | X | | | X | X | X | X | X | X | X | X | | X |
| Investigator Global Assessment (IGA)[13] | X | X | | | X | X | X | X | X | X | X | X | | X |
| Autoimmune Bullous Skin disease Intensity Score (ABSIS)[13] | | X | | | | | | X | | | X | X | | X |
| Assessment of Disease activity questionnaire[13] | X | X | X | X | X | X | X | X | X | X | X | X | | X |

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| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Code Break[17] | | | | | | | | | | | X | | | |
| | | | | | | | | | | | | | | |
| Adverse events, Serious adverse events[18] | Assess continuously from signature of informed consent | | | | | | | | | | | | | |

| **Study Phase** | **Screening** | **Double-blind Period** | | | | | | | | | | **Long term Follow-up**[19] | | **End of study (EoS)** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Visit 1** | **Visit 2 Baseline/Dosing** | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6** | **Visit 7** | **Visit 8** | **Visit 9** | **Visit 10** | **Visit 11** | **Visits 12, 13 and 14** | **V515, V516** | **Visit 777** |
| **Weeks post-dose** | **-** | **0** | **1** | **2** | **3** | **6** | **9** | **12** | **16** | **20** | **24** | **32, 40, 52** | **76, 100** | |
| **Study day(s)** [1] | **-28 to -1** | **1** | **8** | **15** | **22** | **43** | **64** | **85** | **113** | **141** | **169** | **225, 281, 365** | **532, 700** | |
| **Allowed time window** [1] | **-** | **± 2 h for 24 h** | **± 2d** | **± 2d** | **± 3d** | **± 4d** | **± 4d** | **± 4d** | **± 7d** | **± 7d** | **± 7d** | **± 2 weeks** | | |
| Concomitant meds / therapies | Assess continuously from signature of informed consent | | | | | | | | | | | | | |
| Patient diary | | To be completed from Day 1 until EoS | | | | | | | | | | | | |
| Study completion information | | | | | | | | | | | | | | X |

Legend

1. Allowed visit windows are to be scheduled in relation to Day 1 (Baseline/Dosing); Day 1 is the date by which subsequent visits are to be scheduled.
2. Review of inclusion/exclusion criteria, medical history and current conditions, plus measurement of body weight is performed at Baseline, Day 1, prior to dosing.
3. Assessments to be conducted locally at Screening to confirm presence of pemphigus vulgaris (PV) only where not previously performed and documented as part of the patient's regular medical care.
4. Vital signs: Sitting blood pressure and heart rate measurement required at all visits, plus standing measurements only at Screening and Baseline. During study drug administration, blood pressure and heart rate should be obtained every 30 minutes.
5. For women, serum pregnancy testing (human chorionic gonadotropin, hCG) is required screening and end of study regardless of reported reproductive/menopausal status. Urine pregnancy test will be performed at Baseline (Day 1) and every post-dose visit from Week 3 onwards, and may be conducted in addition at the discretion of the investigator or may be required more frequently by local practices, if a menstrual cycle is missed, or if potential pregnancy is otherwise suspected.
6. For postmenopausal women, FSH conducted at Screening to assist in confirming menopausal status.
7. Administration: VAY736 infusion over 1-2 hours following premedication with paracetamol (or acetaminophen) and a H1 receptor blocker.
8. 
9. Commercially Confidential Information
10. 
11. 
12. PK samples on Day 1 to be taken (1) pre-dose, (2) at the end of infusion when the indwelling line is empty and (3) 24 h post-dose (start of infusion: ± 2 h).
13. Assessment completed by the investigator.
14. Assessment completed by the patient.
15. Commercially Confidential Information
16. At the selected sites (refer to footnote 15) this sample will be collected after Week 12 if the IGA score increases by at least 1 compared to the previous visit in patients that have previously reached disease control.
17. At Week 24 the blind will be broken and patients who were on placebo will be offered the opportunity to receive open label VAY736 administration at Week 25, and will follow the same visit pattern as if re-starting from Day 1. Refer to Section 5.5.8 for unblinding prior to Week 24.

18. Serious adverse events are reportable from time of signing informed consent until 30 days after patient has stopped study participation. During the second part of the long-term safety follow-up (from Week 76), only AEs related to VAY736 and/or to infection, potential malignant events and neutropenia will be recorded.
19.

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20.

Note: A patient may reach “disease control” in their PV disease between protocol-defined study visits. In such a circumstance, ad-hoc unplanned clinic visits or consultation over the phone is possible to review/alter a patient’s steroid dose.

21. Pharmacokinetic blood sampling is optional at the end of study

# 1 Introduction

## 1.1 Background

Pemphigus vulgaris (PV) is a very rare chronic autoimmune blistering skin disease caused by autoreactive antibodies that bind to protein components of the desmosome. Within the epidermis, desmosomes play a critical role in maintaining intracellular adhesion between keratinocytes and are important for maintaining the structure and barrier function of skin.

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. Prior to treatment with corticosteroids, the diagnosis of PV was fatal. However, even with current therapy patients with pemphigus vulgaris have an increased mortality with a hazard ratio for death of 3.38 (95% confidence interval 2.21 to 5.17) after adjustment for sex, calendar period, and age group (Langan et al 2008).

The current standard of care for patients with moderate to severe PV is immunosuppressive therapy including oral corticosteroids which are commonly paired with another systemic immunosuppressant such as methotrexate, azathioprine, or mycophenolate mofetil (Feldman and Ahmed 2011). Patients with active disease despite significant therapy or those who are not able to tolerate this therapy are frequently treated with rituximab 'off-label' which has demonstrated efficacy in PV patients in multiple clinical studies and case series. B cell depletion with rituximab, an anti-CD20 monoclonal antibody (mAb) approved for the treatment of rheumatoid arthritis and lymphoma among other indications, leads to a ~65% complete response rate in PV patients across various studies. Furthermore, the safety profile of B cell-depleting therapies has been favorable, even in patients with co-morbidities (Levesque 2009). The dose of rituximab and severity of patient's disease both appear to influence the complete response rate observed in different studies (Feldman and Ahmed 2011). After B cell depletion, most patients experience a remission of disease that can last between 6 and 34 months, but nearly all patients eventually relapse or require additional treatment. A recent publication by Colliou et al demonstrated longer lasting remissions, up to six years, in newly diagnosed PV patients who were treated first line with rituximab due to a contraindication to corticosteroid use (Colliou et al 2013).

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### 1.1.1 Relevant data summary

Detailed background information on the chemistry, pharmacology, toxicology, preclinical and clinical data of VAY736 is given in the Investigator's Brochure. The data most relevant for the present study is summarized below.

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#### 1.1.1.3 Human safety and tolerability data

As of 08-May-2013, human clinical experience with VAY736 is primarily limited to Rheumatoid Arthritis (RA) patients (n = 41, 31 treated) of mild-to-moderate disease severity in an ongoing phase I study CVAY736X2101 designed to assess the safety, tolerability, pharmacokinetics Commercially Confidential Information in single- and multiple-ascending doses of the compound.

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#### 1.1.1.5 Human pharmacodynamic data

Clinical experience to date with VAY736 in autoimmunity is limited to the 41 RA patients in the double blind, randomized, phase 1 ascending SD trial (CVAY736X2101) in which each dose cohort contained 3 patients receiving the active compound and one patient receiving a placebo infusion.

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## 1.2 Study purpose

The purpose of the study is to determine if single i.v. doses of VAY736 can reduce disease activity in PV, determined by the change in Pemphigus Disease Area Index (PDAI) as compared to placebo. The study will also provide the first safety and tolerability information for VAY736 in PV patients.

# 2 Study objectives

## 2.1 Primary objective(s)

- To compare the efficacy of single i.v. doses of VAY736 relative to placebo in reducing clinical disease activity of pemphigus vulgaris patients, as determined by the change in Pemphigus Disease Area Index (PDAI) between baseline and 12 weeks

## 2.2 Secondary objective(s)

- To evaluate the safety and tolerability of VAY736 in patients with PV
- To evaluate the effect of VAY736 in PV patients as assessed by the Autoimmune Bullous Skin disease Intensity Score (ABSIS) at 12 weeks
- To evaluate the effect of VAY736 in PV patients as assessed by Investigator Global Assessment (IGA) at 12 weeks
- To evaluate VAY736 pharmacokinetics in serum in PV patients

## 2.3 Exploratory objective(s)

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# 3 Investigational plan

## 3.1 Study design

This is a non-confirmatory, randomized, partial-blind, placebo-controlled trial evaluating the efficacy, safety, pharmacokinetics Commercially Confidential Information of VAY736 in the treatment of patients with pemphigus vulgaris.

Up to approximately 32 patients will be randomly assigned in a blinded fashion to one of three single dose treatment arms, and at least 24 patients are expected to complete the study. Recruitment will be staggered and progression between doses is dependent upon a safety review milestone (see Figure 3-1).

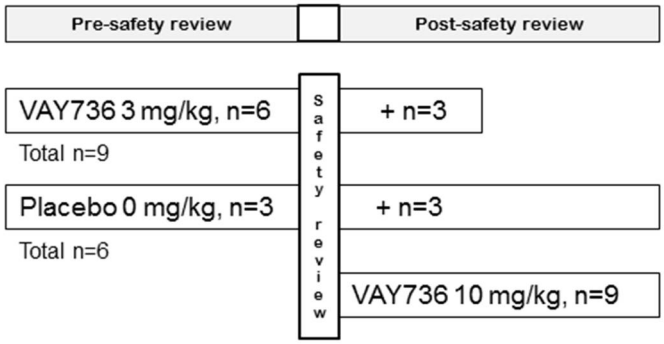
In the pre-safety review period, 9 patients will be randomized to a single dose of either 3 mg/kg VAY736 or placebo (6 dosed with VAY736 and 3 with placebo). After dosing of these 9 initial patients, recruitment will be paused and a safety review will be conducted by an internal Data Monitoring Committee (DMC), independent from the VAY736 project team (see Section 8.4).

The DMC will review all safety data available to the 9$^{th}$ patient achieving Week 6. If there are no safety signals identified by this safety review, recruitment will restart into the 3 mg/kg VAY736 and placebo treatment arms, and will commence to the 10 mg/kg VAY736 treatment arm. If there is a safety signal enrollment will be put on hold, pending a full data evaluation.

Following treatment on Day 1 with study medication, standard of care (SoC) medications are to be maintained at a stable dose level with minimal dose adjustments until "disease control" in signs/symptoms of PV. "Disease control" is defined as the time at which new lesions cease to form and established lesions begin to heal (Murrell et al 2008). A protocol-defined SoC medication taper begins once a patient reaches disease control, to safely deliver the patient to the lowest dose needed to maintain control of their disease (see Section 5.5.5).

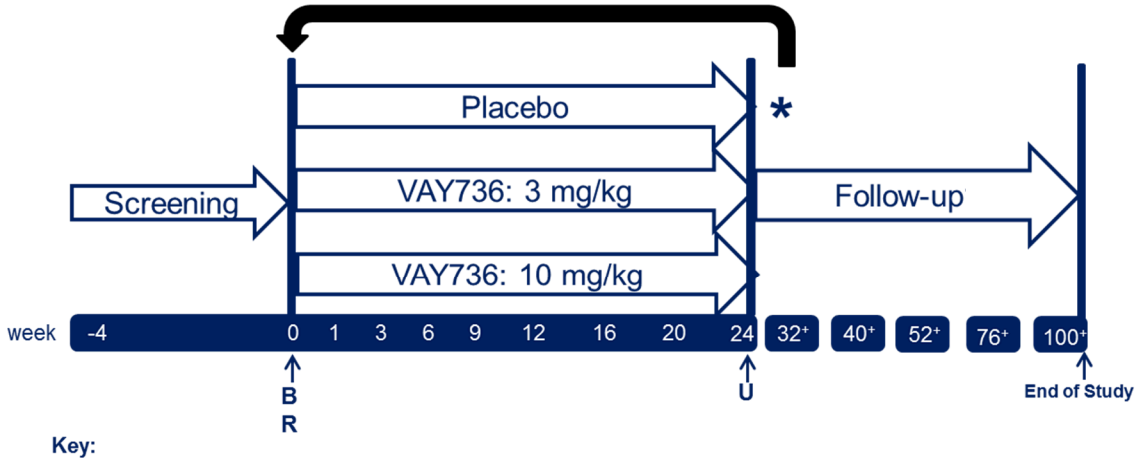
At study completion, it is intended that 9 patients will have been dosed with VAY736 at 3 mg/kg, 9 patients with 10 mg/kg, and 6 patients with placebo.

**Figure 3-1 Study design: Staggered recruitment**




The study will consist of the following Phases (see Figure 3-2):

**Figure 3-2 Study design: Visit Schedule**




**Key:**

**B:** Baseline; **R**: Randomization; **U**: unblinding of patient treatment; *: Placebo patients may enter into open-label VAY736 treatment and restart the study at Day 1

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### Screening Period

The Screening Period consists of a Screening Visit performed within 28 days prior to randomization to assess patient eligibility.

Disease activity will be assessed. Commercially Confidential Information If a confirmation of a diagnosis of PV is required, skin biopsies will be taken and assessed locally only where not previously performed and documented as part of the patient's regular medical care.

### Baseline/Randomization Visit

Following Screening, patients will undergo pre-dose procedures including completion of patient reported outcomes (including visual analog scale [VAS] for

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. In addition, blood samples will be taken for the detection of anti-VAY736 antibodies and other pathway related biomarkers. Digital photographs will then be taken (e.g., torso and extremities) to document disease activity.

Patients will then receive the study drug, which will be administered over approximately a 2 hour period. During this time, the patient will be monitored closely with vital signs taken every 30 minutes. In addition, all patients will receive premedication with paracetamol (or acetaminophen) and a H1 receptor blocker to diminish the signs and symptoms of infusion reactions.

The patient will remain in the study center overnight post-infusion for observation and for measurement of safety parameters, PK samples approximately 24 h post-infusion (start of infusion: ±2 h). Patients will then be discharged from the study site and return as per the schedule described below.

Patients will be given a medication and symptom diary to record any AEs or concomitant medications taken throughout the course of their participation in the study.

No patients shall be infused in parallel at the same time and same center. Treatment of infusion reactions is described under Section 5.5.7.

### Double-blind Period

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A patient may reach “disease control” in their PV between protocol-defined study visits. In such a circumstance, ad-hoc unplanned clinic visits or consultation over the phone is possible to review/alter a patient’s SoC medication dose (see Section 5.5.5).

### Open label administration of VAY736 in Placebo patients

After 24 weeks in the study, at the Week 24 visit (or before in case of early withdrawal from the double-blind period that meets certain conditions – see Section 5.5.8), patients' treatment will be unblinded. When the blind is broken and a patient was assigned to placebo during the double blind period, such a patient will be offered the option to receive open label VAY736 administration from approximately one week after the Week 24 visit, and will follow the same visit pattern as if re-starting from Day 1. Patients will be assigned a new patient number for the open-label treatment. Patients joining the open label part of the study have to satisfy inclusion for active disease and safety labs as mentioned in Section 4, within 2 weeks of their prior Week 24 visit. The dose of VAY736 administered will be 3 mg/kg if a patient reaches Week 24 prior

to the study safety review or 10 mg/kg if dosed after a favorable safety review by the DMC. If a patient prefers not to receive open label active treatment, they are to return within 4 weeks for their EoS visit.

For logistical reasons, it may be necessary for patients to come to the site or a hotel the evening before their scheduled assessment visit, or remain at the site following the visit (e.g. transport restrictions, long travel times from home to site). In these instances, the patients would be hospitalized at the site, but this would not be considered as an SAE.

## 3.2 Rationale of study design

A randomized, placebo-controlled, partial-blind approach is used to eliminate potential bias in reporting safety and biological activity data in this study. The study will be blinded to patients, investigator site staff and the clinical trial team at the time of randomization. Unblinding of patients as they reach the end of double-blind treatment period is planned. This together with the effect of VAY736 on certain assessments may lead to members of the clinical trial team becoming inadvertently unblinded towards the end of the study period.

In addition, the study includes a staggered enrollment to allow progression between the 3 mg/kg and 10 mg/kg to be dependent upon a safety review milestone. The initial 9 patients dosed prior to the safety review will include only the 3 mg/kg VAY736 (n=6) dose and placebo patients (n=3). The rationale for this lower dose group is to confirm that the safety profile in patients with PV with regard to infusion reactions and other short term safety parameters (e.g. chemistry and hematology) is favorable, similar to that observed in study CVAY736X2101. A favorable safety review by the DMC will then enable randomization to commence into the 10 mg/kg dose group and completion of the remaining 3 mg/kg and placebo groups.

In the event that efficacy is observed with both 3 mg/kg and 10 mg/kg, the relationship between dose and parameters of clinical response (e.g., time to remission, duration of remission) can be better explored with a range of doses and exposures offered by these two dose groups.

## 3.3 Rationale of dose/regimen, duration of treatment

Ten (10) mg/kg is the target dose proposed to test efficacy of VAY736 in PV patients in this single i.v. dose study. This dose was safe and well tolerated in the recently completed single dose part of the 3-fold sequential dose escalation phase I study (CVAY736X2101; dose range 0.0003 mg/kg to 10 mg/kg) where it was the maximum VAY736 intended dose administered to RA patients.

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A 3 mg/kg dose will also be tested in the study. The purpose of this lower dose group is to explore a range of drug exposures and provide early dose ranging to understand better the relationship between PK,

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## 3.4 Rationale for choice of comparator

In the current study, placebo will be used as a comparator to provide objective evidence of potential AEs and other safety data, as well as clinical efficacy data generated from patients exposed to the experimental therapy.

The risk of a patient experiencing uncontrolled disease is minimized by continuous use of SoC medication (including azathioprine and mycophenolate mofetil). Furthermore, after unblinding, patients initially randomized to placebo will be offered optional treatment with a single administration of VAY736. The purpose of this optional open label administration of VAY736 is to allow all patients who participate in this study to have an equitable chance to eventually receive study drug.

An active comparator is not included in this study.

## 3.5 Purpose and timing of interim analyses/design adaptations

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## 3.6 Risks and benefits

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Patients treated with VAY736 will experience suppression of a part of their immune system and this carries a theoretical risk of increased infections. In this study, patients with PV will also be exposed to other immunosuppressant agents which are the current standard of care for PV. As patients are required to have PV disease activity to be enrolled in this study, they have a medical need for further treatment in order to suppress their disease. The risk to patients from exposure to multiple immunosuppressant agents will be minimized by a protocol required tapering of these SoC treatments as allowed by their clinical response. Additionally, patients will comply with local requirements for infection prophylaxis (e.g. *Pneumocystis carinii*) that are appropriate for patients on multiple immunosuppressants including B cell suppression.

Other potential risks must be considered with administering VAY736 in humans.

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In addition, hypersensitivity and anaphylaxis are potential risks associated with mAbs.

Patients will be required to have skin sampling by punch biopsy. This procedure is commonly performed in dermatology practice and when performed by a trained medical practitioner carries a minimal risk of infection and bleeding. Minor discomfort and a scar at the site of the biopsy should be expected.

### 3.6.1 Risks associated with immunosuppressants in general

#### 3.6.1.1 Infection

Excessive down-regulation of critical components of the immune system will increase susceptibility to infection. This risk is related to intensity and duration of the immunosuppressive regimen.

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Infections developing in patients exposed to VAY736 should be promptly diagnosed and appropriately treated.

#### 3.6.1.2 Vaccinations

There is currently no data on the influence of VAY736 on response to vaccines in general. Vaccination success may be attenuated under immunosuppressive therapy. It is recommended that, if possible and taking in account the overall status of the patient, potential study participants should complete all pre-planned immunizations in accordance with current immunization guidelines prior to exposure to VAY736.

### 3.6.2 Potential Risks associated with VAY736

#### 3.6.2.1 Late onset neutropenia

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LON has been reported infrequently in association with rheumatologic diseases, with an incidence between 3% and 27% (Wolach et al 2012; Tesfa and Palmblad 2011) and has been associated with treatment of PV (Rios-Fernández et al 2007). LON in patients with rheumatic diseases typically self-resolve rapidly and infrequently results in serious infections. The specific cause of late onset neutropenia remains unknown and rechallenge with rituximab has not led to recurrent neutropenia in previously affected patients.

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### 3.6.2.2 Potential immune-mediated reactions

#### 3.6.2.2.1 Hypersensitivity reactions

The main safety concerns with use of mAbs typically include intolerance

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In addition, excipients in the formulation are present. Either has the potential to result in a hypersensitivity reaction to the formulation. This may clinically manifest in the following ways: acute or delayed allergic reaction, anaphylaxis (very rarely), urticaria, rash, dyspnea and/or hypotension, fever, and chills. VAY736 is a fully human mAb of the IgG1 class. This class of antibody is normally abundant in humans. Therefore, the antibody itself is expected to be less immunogenic in humans than chimeric or humanized antibodies. Assays to detect a putative antibody response to VAY736 are included in the study design.

Serum sickness is a delayed reaction (generally over 4–10 days) to serum proteins or monoclonal antibodies, consisting of a hypersensitivity reaction with immune-complex generation and vascular damage in the skin, joints and kidneys. It occurs especially with chimeric antibody, and its likelihood remains very low for fully human monoclonal antibody.

#### 3.6.2.2.2 Infusions reactions and cytokine release

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Infusion reactions have been experienced by over a third of RA patients exposed to rituximab, with the majority of cases occurring during first exposure when the target cell population is at relatively high levels. Clinical studies with rituximab in PV patients suggest a similar frequency with most reactions being mild and transient (Joly et al 2007). Infusion reactions experienced by RA patients receiving VAY736 as a single intravenous dose up to 10 mg/kg have been limited to mild-to-moderate severity. These reactions occurred in the absence of pre-medication and the resulting signs and symptoms were responsive to treatment with paracetamol.

In the event of an infusion reaction requiring treatment, there should be ready access to intravenous fluids, glucocorticoids, anti-histamines, and acetaminophen as required by the patient's condition. Advanced life support units should also be rapidly accessible within the same facility. In addition, plasmapheresis may be helpful in situations in which decreasing the systemic concentration of VAY736 may be of clinical benefit, based on capacity of plasmapheresis to remove IgG antibody, such as the IgG monoclonal antibody VAY736, from intra- and extra-vascular compartments.

### 3.6.3 Potential Risks associated with SoC medication

### 3.6.4 Corticosteroids

Patients will be allowed to continue to use oral corticosteroids. Corticosteroids are a standard of care treatment for patients with PV. Although commonly used, corticosteroids are hormones and have a risk of systemic adverse events which include, but are not limited to, suppression of adrenal gland function, skin thinning, weight gain, bone weakening, increased risk of infection, and worsening of diabetes among others. The deleterious impact of systemic corticosteroid use on patients with PV has been documented and the risk will be minimized by tapering the steroids if patients are experiencing control of their disease (Mahajan et al 2005).

### 3.6.5 Azathioprine

Patients will be allowed to continue to use azathioprine. Azathioprine is a standard of care treatment for patients with PV and has a risk of adverse effects that includes a risk of cytopenias (e.g., thrombocytopenia, leukopenia, anemia and/or pancytopenia), infections, and gastrointestinal hypersensitivity. These adverse effects can be increased in patients who are sensitized due to low levels of TPMT (thioprine S-methyltransferase) activity. Adverse effects of patients on azathioprine are minimized by testing for TPMT as per standard clinical practice. Patients will be required to follow local prescribing information where applicable and local standards of practice for the use of azathioprine as well as careful monitoring for hematologic toxicity.

#### 3.6.5.1 Mycophenolate mofetil (MMF)

Patients will be allowed to continue to use mycophenolate mofetil (MMF). MMF is a standard of care treatment for patients with PV and has a risk of adverse effects that includes a risk of neutropenia, pure red cell aplasia, gastrointestinal bleeding and infections. Adverse effects of patients on MMF will be minimized by following local prescribing information where applicable and local standards of practice for the use of azathioprine as well as careful monitoring for hematologic toxicity.

# 4 Population

The study population will be comprised of male and female PV patients.

It is planned that up to approximately 32 patients may be enrolled (randomized) into the study; at least 24 patients are expected to complete the study.

The investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all inclusion/exclusion criteria. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a subject from enrollment into the study.

## 4.1 Inclusion criteria

### All patients

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female patients 20 to 70 years of age inclusive (at the time of the Screening visit), and having passed Screening examinations by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests.
3. Diagnosis of PV according to (i) presence of blisters or erosions of the skin or mucous membranes, plus (ii) characteristic documented histological findings in the skin, plus (iii) characteristic findings from direct immunofluorescence in skin

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   If results are not available, biopsies and a blood sample have to be taken at screening to confirm diagnosis.
4. Presence of mild to moderate active PV at Baseline as defined by a PDAI score between 20 and 60 (inclusive) or for a PDAI below 20: an IGA of 2 to 3 (e.g., at least 1% but not more than 10 % BSA involvement).

5. On a stable dose(s) of oral corticosteroid +/- adjuvant therapy of azathioprine or mycophenolate mofetil. Requirements for these standard-of-care (SoC) medications are:
   - Oral corticosteroids alone, with steroid dose to be equivalent to prednisone ≥15 mg per day but no greater than 2 mg/kg/day; or
   - Oral corticosteroid + azathioprine, with steroid dose to be equivalent to prednisone ≥2.5 mg per day but no greater than 1 mg/kg/day, and azathioprine with no specific daily dose requirement; or
   - Oral corticosteroid + mycophenolate mofetil, with steroid dose to be equivalent to prednisone ≥2.5 mg per day but no greater than 1 mg/kg/day, and mycophenolate mofetil with no specific daily dose requirement.
6. SoC medications considered stable if the daily dose has not changed within the 7 days preceding the day of dosing (Day 1) for oral corticosteroid, or within the 14 days preceding the day of dosing (Day 1) for azathioprine and mycophenolate mofetil. Patients must weigh in the range of 40 kg to 150 kg inclusive.
7. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

### Open-label patients (i.e. for placebo-treated patients)

1. Presence of mild to moderate active PV at unblinding, as defined by a PDAI score more than 10.
2. On a stable dose(s) of oral corticosteroid +/- adjuvant therapy of azathioprine or mycophenolate mofetil. Requirements for these SoC medications are:
   - Oral corticosteroids alone, with steroid dose to be equivalent to prednisone ≥15 mg per day but no greater than 2 mg/kg/day; or
   - Oral corticosteroid + azathioprine, with steroid dose to be equivalent to prednisone ≥2.5 mg per day but no greater than 1 mg/kg/day, and azathioprine with no specific daily dose requirement; or
   - Oral corticosteroid + mycophenolate mofetil, with steroid dose to be equivalent to prednisone ≥2.5 mg per day but no greater than 1 mg/kg/day, and mycophenolate mofetil with no specific daily dose requirement.

SoC medications considered stable if the daily dose has not changed within the 7 days preceding the day of dosing (Day 1) for oral corticosteroid, or within the 14 days preceding the day of dosing (Day 1)for azathioprine and mycophenolate mofetil.

## 4.2 Exclusion criteria

### All patients

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study:

1. Use of other investigational drugs at the time of Screening, or within 30 days or 5 half-lives of Screening, whichever is longer; or longer if required by local regulations.
2. Known hypersensitivity to any constituents of the study drug, to murine, chimeric or human antibodies, or to drugs of similar chemical classes (e.g., IgG1 biologics). Also, known hypersensitivity to study drug premedication (paracetamol (or acetaminophen) and H1 receptor blocker).
3. Prior use in the 12 months prior to Screening of any B-cell depleting therapy e.g., rituximab or other anti-CD20 mAb, anti-CD22 mAb, anti-CD52 mAb (patients B cell levels should also have returned to normal, if results are not available, a FACS sample should be taken at screening to confirm).
4. Use of prednisone or other systemic steroids for conditions other than pemphigus vulgaris within the 1 month prior to Baseline.
5. Use of topical steroids (or other topical treatment for PV) within 2 weeks prior to Baseline.
6. Recent previous treatment with phototherapy, biological therapy, immunosupressive agents such as azathioprine (unless it is used as SoC medications for PV treatment as per inclusion criteria # 5), dapsone, or methotrexate. The following washout period will be required for such patients to be eligible to participate in the trial:
   - 6 months washout prior to Screening for IVIg, plasmapheresis, immunoadsorption or i.v. or oral cyclophosphamide;
   - 3 months washout prior to Screening for etanercept, adalimumab, ustekinumab, infliximab or any other immunologically active biologic therapy;
   - 1 month washout prior to Screening for UVB/PUVA therapy, dapsone, methotrexate, and any systemic immunosupressants or other systemic treatment for PV.

   Note: If taking consistent stable dose(s) of allowable standard-of-care (SoC) medications, these are allowable if dose /regimen is maintained throughout the study (refer to Section 4.1 inclusion criterion #5).

   Decisions about management of previous treatments are left to the treating physician in line with the patients' choices, and should be conducted according to local standard of care best practice. The present protocol does not support stopping a medication if the sole purpose is to allow a patient to then become eligible to enter the study.
7. History of major organ or hematopoietic stem cell/marrow transplant.
8. Active viral, bacterial or other infections at the time of Screening or Baseline, or history of recurrent clinically significant infection or of recurrent bacterial infections with encapsulated organisms.

9. Evidence of active or latent tuberculosis (TB), or inadequately treated infection with TB, as defined by the following:
   - A positive QuantiFERON® TB-Gold test at Screening or in the 6 months prior to Screening

   OR
   - A chest radiograph positive for active TB infection at Screening or in the 6 months prior to Screening
   - History of either untreated or inadequately treated latent or active TB infection
     - If a patient has previously received an adequate course of therapy for either latent or active TB infection (according to local standard of care or country guidelines), this is to be documented prior to dosing with study drug.
   - Receiving current therapy for active TB infection
     - If receiving treatment for latent TB infection, a patient may not be excluded, and can potentially be recruited but only with prior approval of the sponsor (in consideration of country incidence rates of multi-drug resistant TB, etc.)
10. Recent vaccination with live/attenuated vaccine within a 2 month period prior to Screening.
11. Current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, psychiatric, or other disease which would make the patient unsuitable for the trial.
12. Significant illness within two 2 weeks prior to initial dosing.
13. History of primary or secondary immunodeficiency, including a positive HIV (ELISA and Western blot) test result.
14. Presence of any malignancy of any organ system that has been under active treatment (e.g., radiation therapy or chemotherapy) within the 2 years prior to Baseline or is anticipated to require treatment during the study period (including follow-up) with the exception of patients with removal of uncomplicated basal cell carcinoma or cutaneous squamous cell carcinoma, who may take part in the study.
15. Screening CBC laboratory values as follows:
    - Hemoglobin <10.0 g/dL
    - White blood cell count <3,000/μL
    - Platelets <100,000/μL
    - Absolute neutrophil count ≤1,500/ μL
16. A positive Hepatitis B surface antigen or Hepatitis C test result at Screening.
17. History of alcohol or substance abuse unless in full remission for greater than 12 months prior to Screening.
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, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 4 months following study treatment. ***Highly effective contraception methods include:***
    - 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.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    - Combination of any two of the following (a+b or a+c, or b+c):
        a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception;
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS);
        c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps which are NOT made of latex) with spermicid, or condom only if in Germany. Note: in Germany, the concomitant use of a condom with spermicidal foam/gel/film/cream/vaginal suppository is not recommended.

    In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

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) 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.

20. Donation or loss of 400 ml or more of blood within eight (8) weeks prior to initial dosing, or longer if required by local regulation.
21. Have any other severe acute or chronic medical or psychiatric condition (e.g., severe mental impairment) or clinical laboratory abnormalities that may increase the risk associated with study participation/treatment or may interfere with interpretation of study results and, in the investigator's opinion, would make the patient inappropriate for entry into this study.

**Open-label patients (i.e. for placebo-treated patients)**

1. CBC laboratory values as follows:
   - Hemoglobin <10.0 g/dL
   - White blood cell count <3,000/μL
   - Platelets <100,000/μL
   - Absolute neutrophil count ≤1,500/ μL

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

# 5 Treatment

## 5.1 Protocol requested treatment

### 5.1.1 Investigational treatment

The investigational drug, VAY736 will be packed by Novartis and supplied to the Investigator as open labeled bulk medication. The dosage form of the supplied drug is lyophilizate in vial and needs to be reconstituted with water for injection (USP or equivalent) and diluted in 5% dextrose infusion bag (USP or equivalent), both provided by the investigator's site. Please refer to Table 5-1 for VAY736 formulation information.

The placebo control selected for this study is the 5% dextrose solution in the infusion bag.

**Table 5-1 Study drug: VAY376**

| Name | VAY736 | Placebo |
|---|---|---|
| Formulation | Powder for solution for infusion (lyophilizate in vial) | NA |
| Appearance before reconstitution | White lyophilized cake | NA |
| Appearance after reconstitution | Opalescent to clear, colorless solution | NA |
| Unit dose | 150 mg per vial* | NA |
| Packaging | 6 mL Type I glass vials | NA |
| Diluent for IV administration | Dextrose 5% in water (USP or equivalent) in 250 mL | Dextrose 5% in water (USP or equivalent) in 250 mL |

* The vials contain a 20% overfill to allow a complete withdrawal of the labeled amount of VAY736

Clinical supplies are to be dispensed only in accordance with the specified study procedures.

An unblinded pharmacist or authorized designee is required to prepare the study drug. Instructions for storage and handling of VAY736 vials, and preparation of VAY736 and placebo infusions are described in the VAY736 Pharmacy Manual (or Dose Preparation Manual), provided as a separate document.

Of note, VAY736 vials require storage between 2-8°C.

### 5.1.2 Additional study treatment

#### 5.1.2.1 Pre-medication

To attenuate severity of infusion reactions, all patients in both study arms will receive the following pre-medication regimen, provided by the study center, prior to the start of the infusion (VAY736 or placebo):

- 1 h prior to infusion: Paracetamol/acetaminophen, 1000 mg orally. Adverse effects from paracetamol/acetaminophen at the listed dose are not expected.
- Directly before infusion: H1 receptor blocker e.g. dimetinden (e.g. Fenistil one to two 4 mL vials at 1 mg/mL) intravenously. Adverse effects of most H1 receptor blockers are mild and can include drowsiness and occasionally gastrointestinal disturbances, dryness of the mouth, vertigo excitation and headaches. The H1 receptor blocker used at each site is to be agreed to by Novartis before the start of the study.

## 5.2 Treatment arms

Patients will be randomized to one of the following 3 treatment arms, defined as:

- VAY736 active: single i.v. dose of 3 mg/kg VAY736 from infusion bag containing the active compound on Day 1
- VAY736 active: single i.v. dose of 10 mg/kg VAY736 from infusion bag containing the active compound on Day 1
- VAY736 placebo: single i.v. dose from infusion bag without active compound on Day 1

The overall randomization ratio will be 3:3:2. Before the first IA and safety review 9 patients will be randomized to the above treatments in a ratio of 2:0:1. After the safety review the remaining patients will be randomized in a ratio of 1:3:1.

### Open label

Patients entering the open label cohort will be assigned to receive

- VAY736 active: single i.v. dose of 3 mg/kg VAY736 from infusion bag containing the active compound on Day 1 if blind is broken prior to the completion of the safety review
- VAY736 active: single i.v. dose of 10 mg/kg VAY736 from infusion bag containing the active compound on Day 1 if blind is broken after the completion of the safety review

## 5.3 Treatment assignment

Randomization numbers will be assigned in ascending, sequential order to eligible subjects (see Section 5.5.1 for details). The investigator will enter the randomization number on the CRF.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme for subjects will be reviewed and approved by a member of the Novartis IIS Randomization Group. Numbers

between 5101 and 5112 will be used before the safety review. Numbers between 5113 and 5132 (or higher) will be used after the safety review.

### Randomization Procedure for central management of randomization numbers:

When an eligible patient at a participating study site is ready to be randomized into the study, the steps below will be followed:

1. The site designee will complete a Randomization Request form and fax or email to the Novartis designee.
2. On receiving, the Novartis designee will write the next available randomization number within the randomization list for the corresponding part of the study on the form and fax or email back.
3. On receiving the allocated randomization number, the unblinded pharmacist or authorized designee will use the information on the completed form to ensure that the patient receives the correct study medication, according to the provided randomization list.
4. After inclusion of each new patient, the site designee will countersign the Randomization Request form, and fax or email it back to the Novartis designee to document the correct assignment of the patient's randomization number and the date the patient received their first dose of study medication.

The site designee will enter the randomization number on the CRF.

## 5.4 Treatment blinding

This is a partial blind study: subjects, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of study treatments at the time of randomization and during the double-blind treatment period according to the specifications provided in Appendix 4. Randomization data are kept strictly confidential until the time of unblinding for the respective person(s) with the following exceptions:

- The pharmacist charged with preparing and distributing infusion solutions containing VAY736 or placebo
- The medical monitor/Investigator at the site, independent to the study, who will review the hematology panel including differentials results throughout the study
- The unblinded monitor source data verifying the hematology panel and monitoring drug accountability

The PK bioanalyst will be unblinded during the clinical study, but will not provide individual PK data prior to data-base lock, except in case of an interim analysis happening after all patients have completed Week 24 and all team members, investigators and patients have been unblinded.

In order to help reduce the risk of unblinding that might arise if an infusion reaction occurs, all patients will receive treatment with paracetamol/acetaminophen and a H1 receptor blocker prior to infusion with VAY736.

An unblinded pharmacist at the investigator site will prepare the study treatment for infusion from the bulk open-labeled supplies. The diluent (dextrose 5% in water solution) serves as placebo and will not contain VAY736.

the hematology laboratory evaluation results will be concealed from the Investigators and patients in order to maintain the study blind. The necessary safety review may lead to the Novartis study team being inadvertently unblinded, however this information will not be communicated to the investigator.

Investigators and patients will be unblinded to treatment assignment after Week 24 (or earlier see Section 5.5.8) visit in order to propose open-label administration of VAY736 to the placebo arm.

Further unblinding will only occur in the case of subject emergencies (see Section 5.5.12), at the time of the interim analysis and at the conclusion of the study.

Further information regarding blinding (and unblinding) is presented in Appendix 4.

## 5.5 Treating the subject

### 5.5.1 Subject numbering

#### Screening number

Each subject screened is assigned a unique screening number. The screening number is a combination of the center number that is provided by Novartis, and a five digit number starting with 00001 for each subject which is assigned by the Investigator. Therefore, if the center number is 1001 the screening numbers will be assigned such as 100100001, 100100002, 100100003 in ascending order. If the center number is 1002, the screening numbers will be 100200001, 100200002, 100200003 in an ascending order.

#### Randomization / treatment number

If the patient is deemed eligible for the study and will commence dosing, a randomization number will be assigned. Once assigned to a patient, a randomization number will not be reused.

The randomization number becomes the definitive subject number as soon as a patient receives the first dose of the respective study treatment.

There should be a source document maintained at the site which links the screening number to the randomization assignment number (once assigned). This source document should be provided to all appropriate parties (i.e. Central Laboratory, ECG Laboratory) as soon as this is available.

Randomization numbers will be generated for 32 (or more) to allow for approximately 24 subjects to complete the study. Subjects will be assigned randomization numbers, 5101-5132. Numbers between 5101 and 5112 will be used before the safety review. Numbers between 5113 and 5132 (or higher) will be used after the safety review.

Placebo patients entering the open-label part cohort will be issued with a new randomization number. These patients will be assigned randomization numbers, 7101-7130. If a patient joins the open-label VAY736 part, the new randomization number assigned will correspond to the original randomization number (e.g. patient 5103 would be assigned 7103).

The table below summarizes the general details of the numbering of the patients once randomized to treatment:

**Table 5-2 Patient Numbering**

| Part | Randomization Number |
|---|---|
| Single dose (pre-safety review) | 5101 – 5112 |
| Single dose (post-safety review) | 5113 – 5132 (or higher) |
| Open label | 7101 – 7132 (or higher) |

### 5.5.2 Dispensing the study treatment

The investigational drug, VAY736 will be prepared by Novartis and supplied to the unblinded pharmacist / technician at the Investigator's site as open labeled bulk medication of several 6 mL glass vials.

For preparation of the study medication, a copy of the randomization list will be sent to the unblinded pharmacist / technician at the Investigator's site.

Clinical supplies are to be dispensed only in accordance with the specified study procedures. Appropriate documentation of the subject specific dispensing process must be maintained.

Bulk medication labels will be in the local language, will comply with the legal requirements of each country, and will include storage conditions for the drug but no information about the subject.

### 5.5.3 Handling of study treatment

#### 5.5.3.1 Handling of investigational treatment

Investigational treatment must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated staff have access. Upon receipt, the study drugs should be stored according to the instructions specified on the labels.

Storage conditions (2-8°C) must be adequately monitored and appropriate temperature/logs maintained as Source data.

The unblinded pharmacist and Investigator are accountable for ensuring maintenance of an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be noted by the unblinded Monitor during site visits and/or at the completion of the trial.

All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novartis, the Investigator must not destroy any drug labels, or any partly used or unused drug supply.

At the conclusion of the study, and, if allowed during the course of the study (e.g. an open label study or an unblinded monitor), the Investigator will provide a copy of the drug accountability ledger to the Monitor.

Only after receiving a written authorization by Novartis, the Investigator/designee will send all the unused and partly used drug supplies as well as the empty containers to the address provided at the time of authorization for destruction or have the unused and partly used drug supplies as well as the empty containers destroyed by the site's pharmacist, providing a drug destruction certificate.

#### 5.5.3.2 Handling of other study treatment

**Pre-medication**

In order to reduce the chance of infusion reactions and subsequent potential unblinding, patients will be administered paracetamol/acetaminophen and a H1 receptor blocker before the infusion. Details are given in Section 5.1.2.1. Use of pre-medication will be monitored.

**Standard of Care (SoC) medications**

Following treatment on Day 1 with study medication, SoC medications are to be maintained at a stable dose level until "disease control" in signs/symptoms of PV. Limited changes to a patient's dose of SoC medications will be allowed. Details are given in Section 5.5.5.

Use of SoC medication will be monitored.

The medications needed for pre-medication and allowed for treatment of adverse reactions and PV SoC medications are not considered study supplies and therefore need to be supplied by the study site or treating physician.

### 5.5.4 Instructions for prescribing and taking study treatment

The study medication VAY736 will be administered as an i.v. infusion over approximately 2 hours by the study center personnel following the instructions and using the material as described and specified in the VAY736 Pharmacy Manual.

Any update to the Pharmacy Manual describing the preparation of additional doses will be provided as needed directly to the study center personnel.

Presence of a physician at the patient bedside will be expected during the infusions. Unless performing a study assessment, patients should rest quietly for the next 2 hours under medical observation.

All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the Dosage Administration Record (e)CRF.

### 5.5.5 Taper of Standard of Care (SoC) medications

Following treatment on Day 1 with study medication, SoC medications are to be maintained at a stable dose level until disease control in signs/symptoms of PV. Limited changes to a patient's dose of SoC medications will be allowed as described in the following paragraphs.

Control of disease activity or "disease control" is defined as the time at which new lesions cease to form and established lesions begin to heal (Murrell et al 2008 – see Section 6.4.4).

Once disease control is achieved, as defined above, a patient's dose of SoC medications are to be kept stable for a minimum of 2 weeks and at the end of this period if no new lesions have developed and the majority (~80%) of lesions have healed, the patient will begin a protocol-defined corticosteroid taper to safely deliver the patient to the lowest dose needed to maintain control of their PV.

- If a patient reached disease control between protocol-defined study visits, ad-hoc unplanned clinic visits or consultation over the phone is possible to review/alter a patient's steroid dose
- Ad-hoc unplanned clinic visits or consultations with a patient over the phone are also possible during the SoC medication taper, at the discretion of the investigator (e.g., evaluate worsening of disease or adjust dose)

The prednisone will be tapered according to the following instructions:

- reduce the daily dose by 20 mg every week until reaching a daily dose of 40 mg,
- reduce the daily dose by 10 mg every week from a daily dose of 40 mg down to 10 mg,
- once the daily dose of 10 mg has been reached, the taper will be determined by the investigator.

If the patient has been placed on steroids as short-term treatment and the prednisone can be safely discontinued the following week, then this is recommended. If the patient has been on steroids chronically and will require a slower taper after reaching 10 mg/day then the investigator should consider decreasing the dose to 5 mg the following week with the remaining taper to be determined by the patient's response. At each visit after initiating the steroid taper, a patient is eligible to continue with a steady decrease in their steroid dose if disease control continues and no evidence of steroid withdrawal is observed (e.g., fatigue, weakness, nausea, anorexia, hypotension, body aches or joint pain). Dose adjustments as required by the steroid taper will take place weekly, regardless of the visit schedule, and in the event that patients require consultation with the investigator this can take place as an ad-hoc unplanned visit or telephone conversation.

If a patient has worsening symptoms or evidence of steroid withdrawal then the patient is considered to have failed their taper and the steroid dose will either be maintained or increased to the minimum dose considered adequate by the investigator to control the patient's symptoms (e.g., the previous dose that was tolerated and offered control of PV disease activity – see Section 5.5.8). In the event that a patient fails the protocol defined tapering regimen multiple times, then the investigator can introduce a tapering regimen to safely bring the patient to the lowest amount of SoC medication as quickly as possible.

A taper of SoC medication adjuvant to oral corticosteroid (e.g., MMF or azathioprine) is to be started only after the steroid dose has been successfully decreased such that it is approximately 5 mg per day or less and has been maintained at this level for one month. Azathioprine or mycophenolate mofetil are to be tapered such that the dose is decreased by approximately 25% every 4 weeks. Changes to such medication dose/regimen are preferred at protocol-defined or ad-hoc study visits rather than by consultation with a patient over the phone (as was possible for steroid tapering).

### 5.5.6 Permitted dose adjustments and interruptions of study treatment

In case of suspected infusion reaction, the infusion can be stopped for 30 minutes and the patient observed to determine the severity of the reaction. Depending on the assessment of the patient, symptomatic treatment can be administered and the infusion can be restarted at a reduced rate if necessary.

These changes must be recorded on the Dosage Administration Record CRF.

### 5.5.7 Recommended treatment of adverse events

Potential adverse events should be treated symptomatically.

Intravenous administration of mAbs can be associated with infusion reactions secondary to hypersensitivity, Commercially Confidential Information . Most infusion reactions occur within the first 2 hours of mAb exposure. In this study, VAY736 will be infused over a 2 hour period. During this period, administration of VAY736 can be modified and clinical treatment provided as determined by the treating physician on a case-by-case basis. The following guidelines are provided using the National Cancer Institute Common Toxicity Criteria for allergic reaction, anaphylaxis and cytokine release [NCI-CTCAE/v4.03, Reference http://evs.nci.nih.gov/ftp1/CTCAE/About.html].

In the case of a suspected infusion reaction, the infusion can be stopped for 30 minutes and the patient observed to determine the severity of the reaction. Depending on the assessment of the patient, medication can be administered and the infusion can be restarted at a reduced rate if necessary. Additional guidance on severity grading and treatment includes the following:

- Mild National Cancer Institute (NCI) grade 1 infusion reactions do not require treatment.
- In case of moderate NCI grade 2 infusion reactions requiring symptomatic treatment, the patient can be treated with anti-histamines, NSAIDs, paracetamol/acetaminophen, intravenous fluids) as determined by the investigator, but only while adhering strictly to the maximal daily dose limits of these medications. The infusion can be stopped for 15 minutes and then restarted at a reduced rate.
- In case of more severe NCI grade 3 or 4 reactions, the infusion should be stopped and corticosteroids according to local guidelines administered intravenously.
- Other available medications at the bedside should include paracetamol/acetaminophen, adrenaline, bronchodilators, and /intravenous preparations of anti-histamines.

Infusion reactions of severity NCI grade $\geq$ 2 despite pre-medication with paracetamol/acetaminophen and an H1 blocker may require modification of the pre-treatment regimen. Medication to prevent or treat the signs and symptoms of infusion-related reactions will be provided by the study site.

Plasmapheresis may be helpful in situations in which decreasing the systemic concentration of VAY736 may be of clinical benefit, based on capacity of plasmapheresis to remove IgG antibody, such as the IgG monoclonal antibody VAY736, from intra- and extra-vascular compartments.

In the case of severe neutropenia requiring treatment, filgrastim (granulocyte colony-stimulating factor analog; G-CSF) may be used to stimulate the proliferation and differentiation of granulocytes.

In the case of clinically relevant hypogammaglobulinemia, an intervention may be required such as replacement by Intravenous Immunoglobulin (IVIG).

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies (e)CRF.

### 5.5.8 Rescue medication

Except the patient's Standard of Care treatment (SoC; oral corticosteroid +/- adjuvant therapy) described in Section 5.5.5, no additional rescue medication is allowed; however, adjustment to a patient's SoC is allowable, with certain conditions, for a patient to remain on study.

During the Double-blind period (Weeks 0 to 24), adjustment of SoC is limited to one (1) increase (either corticosteroid or adjuvant therapy alone or both on the same day) in the first 24 weeks if the IGA score worsens by 1 point or more With one increase, a patient can continue on the study without change to the study visit schedule.

If a patient has already had an increase in oral corticosteroid or in adjuvant immunosuppressive drugs (azathioprine or mycophenolate mofetil) and is still experiencing a disease flare up that in the Investigator's opinion requires intervention (e.g., IGA score worsens by a further 1 point or more from the prior SoC increase timepoint), then depending on when this second increase of SoC happens the patient should follow the schedule below:

- Second increase in SoC up to & including Week 12 – Patient to return and complete visits up to & including the Week 12 visit. Treatment to be unblinded early at the Week 12 visit.
- Second increase in SoC after Week 12 – Patient to return and skip forward to complete the Week 24 visit assessments. Treatment to be unblinded early (at the time of SoC increase or at the Week 24 visit).

Following this early unblinding, a patient on placebo is to be offered the opportunity of open label VAY736, whereas a patient on VAY736 would enter the long-term follow-up period (from Week 32 onwards). Similarly, if a patient previously on placebo prefers not to receive open label active treatment, they are to return within 4 weeks for their EoS visit

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If more than two increases of SoC treatment are required in an aim to control a patient's disease symptoms, such a patient will already have been withdrawn from the double-blind period and skipped forward to be monitored in the long-term follow up period following the second increase in SoC. Such patients would already have had their treatment unblinded after the second increase. These patients should continue to return for the visits/assessments in the long-term follow up period (from Week 32 onwards).

For all patients, regardless of any increase(s) to SoC treatment(s), the duration of the long-term follow up and determining when End of Study (EoS) takes place is to follow the decision tree in Appendix 5.

If worsening occurs in-between visits – the investigator or study staff are to request the patient return to the site for an ad-hoc unplanned visit to be evaluated; alternatively, for corticosteroid dose adjustment only, consultation over the phone is also possible.

SoC dose and any failure of a patient to progress in their taper will be captured at every visit in the (e)CRF.

### 5.5.9 Concomitant treatment

The investigator should instruct the subject to notify the study site about any new medications he/she takes after the start of the study drug.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

### 5.5.10 Prohibited treatment

Use of the treatments displayed in the table below is NOT allowed after screening.

If, nevertheless, any of the below mentioned medication is taken during the study, a patient has either to be withdrawn from the study in case they are in the double-blind part or can stay in the study if they stop immediately the medication if such medication(s) have a short half-life or a minimal impact if taken punctually (see Table 5-3).

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**Table 5-3 Prohibited treatment**

| Medication | Action |
|---|---|
| IVIG, plasmapheresis | Withdraw from double-blind period, unblind treatment and follow-up for safety |
| I.V. or oral cyclophosphamide | Withdraw from double-blind period, unblind treatment and follow-up for safety |
| Rituximab | Withdraw, unblind treatment and follow-up for safety. If taken after Week 24, patient should go directly to EOS visit. |
| Etanercept, adalimumab, ustekinumab, infliximab or any other immunologically active biologic therapy | Withdraw from double-blind period, unblind treatment and follow-up for safety |
| UVB/PUVA therapy | Discontinue phototherapy |
| Azathioprine, mycophenolate mofetil (if not part of SoC medication from Screening), dapsone, methotrexate, and any systemic immunosupressants or immunomodulators | Discontinue medication |
| topical corticosteroids | Discontinue medication |
| topical calcineurin inhibitors (e.g., elidel) | |

### 5.5.11 Discontinuation of study treatment and premature subject withdrawal

**Study "Stopping rules"**

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However, infusion reactions (hypersensitivity, cytokine release, anaphylaxis) can occur with administration of biologics,

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. Increased susceptibility to infection is also a potential risk with therapies targeting elements of the immune response. Thus for patients on active treatment, the following guidance and stopping rules are provided:

Dose limiting toxicities (DLTs) will be assessed according to the standardized toxicity grading scale, the NCI Common Toxicity Criteria for Adverse Events [NCI-CTCAE/v4.0, Reference http://evs.nci.nih.gov/ftp1/CTCAE/About.html]. Although the stopping criteria will not incorporate an absolute requirement for causality, the potential relationship between an adverse event and VAY736 will be evaluated carefully on a case-by-case basis.

**Overall study:**

The study will be stopped if any of the following criteria are met, and no further patient will be dosed pending a full safety review:

- Any treatment-related death
- Decrease in neutrophil count:
  a. If any subject requires G-CSF or GM-CSF treatment for neutropenia, or
  b. If two or more subjects manifest a persistent neutrophil count <500 cells/uL, or
  c. If four or more subjects manifest a persistent neutrophil count <1000 cells/uL
- More than 1 infusion reaction of grade 3 severity of the NCI-CTCAE/v4.0 Criteria within the first 5 treated subjects and an incidence of >20% thereafter
- Any treatment-related, grade 3 toxicity of the NCI-CTCAE/v4.0 Criteria with the following exceptions:
  - Events of Special Interest, including infusion-related (hypersensitivity, cytokine release, anaphylaxis), decreased neutrophil or leukocyte counts not requiring treatment, and diagnostic procedures involving elective or non-urgent hospital admission
  - Disease Specific Events that are due to the patients underlying PV diagnosis
  - AE/SAEs unrelated to the experimental compound as assessed by the investigator or Novartis
- Clinically significant (according to the investigator) and study drug-related, persisting changes from baseline in vital signs, electrocardiograms, or medically relevant, persistent changes in laboratory parameters, which are not consistent with existing co-morbidities, in >1 patient within the first 5 treated subjects and an incidence of >20% thereafter
- It is indicated by the early safety review of the first 9 patients (Section 3.1). In the event of an unfavorable safety review, the study will not progress to dose further patients but the 9 patients will continue in the study until EoS as planned
- Other clinically significant changes or effects in the opinion of the Investigator or Sponsor that are deemed unsafe to continue dosing

In addition all blinded safety data, including events of special interest and disease specific events, will be evaluated by the Sponsor and PI continuously and at scheduled meetings. The study may be put on hold pending further data analysis, and the decision to adjust the dose or modify the pre-medication if the following criteria occur:

- The principal investigator or the Sponsor considers that the number and/or severity of AEs justify discontinuation of the study.
- Other clinically significant changes or effects in the opinion of the Investigator or Sponsor that are deemed unsafe to continue dosing.

The study can also be terminated at any time for any reason by Novartis. Should this be necessary, the Investigator will be informed of the procedures to be followed to assure that adequate consideration is given to the protection of the patient's interests. The Investigator will be responsible for informing IEC / IRB's of the early termination of the trial.

### Individual subject withdrawal

Due to the single dose nature of the study, no individual treatment stopping rules are provided

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 patient withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient'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 patients' treating physician/obstetrician

Patients who withdraw prior to Week 12 should return for the Week 12 visit before skipping forward to enter the long term follow up period. Patients who withdraw after the Week 12 visit yet prior to Week 24 should return for the Week 24 visit before entering the long term follow up period (after Week 24). During the long term follow up period, patients will have visits according to the following schedule Commercially Confidential Information until up to 2 years after last dose, unless the patient starts another immunomodulatory or immunosuppressive treatment:

- Every 8 weeks until the Week 40 visit
- A Week 52 visit
- Every 24 weeks until Week 100 visit

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The End of Study visit will include study completion evaluations followed by discharge from the study.

Patients who withdraw after Week 24, during the long term safety follow up period, will be asked to return and complete the end of study visit. Commercially Confidential Information

For subjects who are lost to follow-up (i.e. those subjects 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 subject, e.g. dates of telephone calls, registered letters, etc.

### 5.5.12 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. A complete set of emergency code break cards will be provided to the investigator site(s) and a complete set will be available at Novartis. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secure place but be accessible in case of emergency. The investigator will receive a blinded code break card for each subject, with the details of drug treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason other than an emergency. When the investigator removes the scratch-off cover he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. **The unblinded treatment code should not be recorded on the CRF.** The investigator must also immediately inform the Novartis local monitor that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the code break cards in case of emergency. If appropriate, the investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable.

An assessment will be done by the appropriate site personnel and the sponsor after an emergency unblinding to assess whether or not the patient should be withdrawn from the study.

After 24 weeks in the study, at the Week 24 visit (or before in case of early withdrawal from the double-blind period that meets certain conditions – see Section 5.5.8), patients' treatment will be unblinded. The patient will be informed of the treatment group; if the patient has been treated with placebo, (s)he will be offered the optional open label VAY736 administration.

### 5.5.13 Study completion and post-study treatment

Each subject is expected to complete the study in its entirety and thereafter no further study treatment will be made available to them. The study will complete when the last subject completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

#### 5.5.13.1 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patients should be seen as soon as possible and treated as prematurely withdrawn subjects.

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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 subject's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

Should the study be terminated, patients assigned to placebo group will not be offered the optional VAY736 administration.

# 6 Visit assessments

The full assessment schedule is presented at the end of the synoptic section, above.

Subjects should be seen for all visits on the designated day with an allowed "visit window" of:

- +/- 2 days for Day 8 (Week 1) visit, Day 15 (Week 2) visit
- +/- 3 days for Day 22 (Week 3) visit
- +/- 4 days for Day 43 (Week 6), Day 64 (Week 9), Day 85 (Week 12) visits
- +/- 7 days for Day 113 (Week 16), Day 141 (Week 20), Day 169 (Week 24) visits
- +/- 2 weeks for all additional visits for the safety follow-up period Commercially Confidential Information or up to 2 years after last dose, unless the patient starts another immunomodulatory or immunosuppressive treatment)

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The End of Study visit will include study completion evaluations followed by discharge from the study.

Subjects, who discontinue before completing the study, and those who prematurely withdraw from 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.

Deviations for the following assessment times are acceptable based on logistical and operational considerations:

### PK sampling

PK samples should be collected as per the assessment visit schedule.

On visit where the treatment is given, PK samples should be collected:

- Pre-dose, before start of the infusion
- At the end of infusion when the line is empty for the 2 h post-dose samples
- 24 h post-dose (start of infusion: +/- 2 h)

### ECG, Vital signs

ECG and Vital signs measurements should be performed:

- Up to 2 h pre-dose
- As per the Assessment schedule

### Other samples

- Safety laboratory, blood biomarker should be taken up to 24 h pre-dose.

Every effort will be made to take the pharmacokinetic sample at the protocol specified time. Other assessments e.g. ECG, vital signs etc will be taken prior to / after the pharmacokinetic sample.

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## 6.1 Dietary, fluid and other restrictions

On dosing days, patients should not eat for about 1 hour after the end of the infusion. Unless performing a study assessment, patients should rest quietly for the next 2 hours.

Due to the use of Standard of Care adjunct medications it is requested that patients moderate their intake of alcohol and may be required to abstain from alcohol if needed for concomitant medications. No other restrictions are required on the study.

## 6.2 Subject demographics/other baseline characteristics

### Demographics

Subject demographic and baseline characteristic data to be collected on all subjects include: date of birth, age, sex, race, predominant ethnicity.

### Relevant Medical history / Current medical conditions

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, diagnoses and not symptoms will be recorded.

### PV history and previous PV treatment

Details of the diagnosis, past medical history and previous treatments related to PV and other autoimmune diseases will be collected and entered into the CRF.

### Prior and Concomitant Medication/Significant Non-Drug Therapies

All concomitant medications taken or other therapeutic interventions executed within 30 days prior to Screening and during the study must be recorded. Both the start date and the end date for each medication should be captured on the “Concomitant Medications/Significant Non-Drug Therapies” eCRF page.

### Hepatitis screen, HIV screen

Patients will be screened for Hepatitis B surface antigen. Screening for Hepatitis C will be based on Hepatitis C virus 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.

The decision whether to re-test patients for hepatitis and HIV should be based on the patient's individual risk and history and should take the duration between completion of the core study and enrollment in the extension study into account.

Results will be available as source data and will not be recorded in the eCRF.

### Alcohol test, Drug screen

Subjects will be tested for substances of abuse (e.g., alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates). Sample should be sent to central lab for analysis.

Results will be available as Source data and will not be recorded in the eCRF.

### Testing for tuberculosis

Testing for tuberculosis will be performed and read at Screening or accepted up to 6 months prior to screening.

Tuberculosis testing should be performed with the QuantiFeron test. Should a study site not have access to the QuantiFeron test, a chest X-ray can be performed instead of the QuantiFeron test.

**Chest X-ray**: If deemed necessary a standard chest X-ray will be performed. The subject identifier and date of chest X-ray must appear on each film. The report will be dated and signed by the person who makes the interpretation. Historically signed reports will be acceptable, provided the film is archived at the site. The original X-ray film, appropriately labeled, will be archived at study site.

Precaution 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).

Data will be stored as source data and not collected in the eCRF.

### Study completion information

Information on the date the subject last took drug, the subject completion or discontinuation of the study and the reason for discontinuation of the study will be recorded on the Study Completion eCRF page.

Study Completion evaluations must also be performed when a subject prematurely withdraws from the study for whatever reason.

### Comments

All comments related to study conduct will be added to the eCRF

## 6.3 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with VAY736, as detailed in Section 6.6.

All doses dispensed to the subject during the study must be recorded on the Dosage Administration Record. Date and time of dose administration will be recorded in the Dosage administration record section of the eCRF.

## 6.4 Efficacy / Pharmacodynamic assessments

### 6.4.1 Pemphigus Disease Area Index (PDAI)

The PDAI is a specific cutaneous and mucosal disease activity assessment performed by the investigator based on the evaluation of lesions in well-defined anatomical locations (Pfütze et al 2007; Murrell et al 2008; Rosenbach et al 2009; Daniel et al 2012).

The score is weighted for the number and size of lesions with a score of 0 (absent) to 10 given for skin (12 body locations), scalp and mucous membrane showing disease activity (erosions/blisters or new erythema). To be more precise at the lower end of the PDAI score the value of 1 that included 1-3 lesions on each anatomic region is split in intervals: 1 corresponds to one lesion (none greater than 2 cm); 1.3 corresponds to two lesions and 1.6 corresponds to three lesions.

Damage, such as post inflammatory hyperpigmentation or erythema from resolving lesion, is scored separately from the main score as absent (0) or present (1) for each body area or scalp resulting in a score of 0 to 12 or 0 to 1, respectively.

Therefore the PDAI score ranges from 0 to 263, with 250 points representing disease activity (120 points for skin activity; 10 points for scalp activity; 120 points for mucosal activity) and 13 points representing disease damage. Please refer to the PDAI scoring sheet in Section 18-Appendix 6.

The investigator will complete a paper copy of the scale, which will serve as source data and the subject's responses will be transcribed into the CRF.

### 6.4.2 Autoimmune Bullous Skin disorder Intensity Score (ABSIS)

The ABSIS Score is a quality- and quantity-based score for cutaneous and oral mucosal lesions combining the extent of the affected body surface area (BSA), the quality of the skin lesions and oral involvement (Pfütze et al 2007; Rosenbach et al 2009; Daniel et al 2012).

The cutaneous involvement score consists of the percentage of affected BSA and a weighing factor describing the quality of lesions. To define BSA of involved skin the palm is used as a scoring help: it is assumed that the patient's palm without fingers is 0.5% of BSA. This differs from the original guidance of ABSIS for reason of being consistent in this study, and has no impact on the accuracy of calculation of BSA. Each body part equals 9% or a multiple of 9% of BSA, such that in adults the head and neck is 9%, one arm (including the hand) is 9%, the trunk is 36%, one leg is 18%, and the genitals are 1%, please refer to Section 19-Appendix 7 for an illustration of BSA assessment A weighting factor of 1.5 is used for erosive, exudative lesions, whereas erosive, dry lesions have a weighting factor of 1.0 and re-epitheliazed lesions (excluding post-inflammatory erythema and/or hyperpigmentation) have a weighting factor of 0.5.

Oral involvement scores the extent of lesions (absence: score of 0; presence: score of 1) and their severity addressed as discomfort during eating and drinking for 11 different parts of the mouth. These 11 sites include upper and lower gingival mucosae, upper and lower lip mucosae, left and right buccal mucosae, the tongue, floor of the mouth, hard and soft palate, and the pharynx. The severity of oral lesions is assessed by the amount of pain/bleeding associated with certain foods. The food categories listed in the table are examples for the different food levels and may vary by country, the food level (1-9) will remain the consistent reference for analysis purposes. The factor discomfort is attributed a score of 0, 0.5, or 1 for the symptoms of never experiencing problems, pain/bleeding occurring sometimes, or pain/bleeding occurring always, respectively. The final severity score is the summation of the products of the food-specific score multiplied with the factor of discomfort. The maximum scores for oral involvement are 11 for extent and 45 for severity. Please refer to Section 20-Appendix 8 for an example of the ABSIS scoring sheet.

In summary, the ABSIS score ranges from 0 to 206 with 150 points for skin involvement, 11 points for oral involvement and 45 points for subjective discomfort during eating and drinking.

### 6.4.3 Investigator global assessment (IGA)

An IGA score on a 0-4 scale will be used to assess each patient’s PV disease activity as per the scale in Section 21-Appendix 9 (modified from Mahajan et al 2005). IGA scores will be captured in the eCRF.

For the IGA, active PV lesions are defined as urticarial lesions, blisters and erosions which are not epithelialized. Erythematous patches and erosions which have healed to the extent that they are epithelialized are not included in the body surface area assessment (BSA). For the estimation of BSA, the palm of the patient (not including the surface of the fingers) is considered to be 0.5% of the total BSA (Agarwal and Sahu 2010).

### 6.4.4 Disease activity

At each visit the investigator will assess the phase of the patient's disease activity according to the following:

**Uncontrolled phase** – new lesions continue to form

**Controlled phase ("Disease Control")** - new lesions are not forming and established lesions are beginning to heal

**Post-consolidation phase** – new lesions have not developed for a minimum of 2 weeks and approximately 80% of lesions are healed

**Complete remission on SoC therapy** - absence of new or established lesions while on SoC therapy

**Complete remission off SoC therapy** - absence of new or established lesions and no SoC therapy

This assessment will be documented at each visit using a source paper CRF, which will then be transcribed into the eCRF.

If disease control was achieved between planned study visits, then the date of disease control will be captured in the eCRF.

Details of changes in SoC medication will be recorded in the eCRF.

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## 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, 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.

Signs and symptoms of infection (e.g., pneumonia, cellulitis, lymphadenopathy) should be given special attention during the physical examination due to the immune suppression of the patient population.

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 Clinical scrutiny to minimize the risk of infection

Patients will be carefully monitored for clinical signs and symptoms and for clinical chemistry / hematology results suggestive of an infection on a regular basis during treatment and until Study Completion, as part of the broader safety monitoring (refer to Section 7).

### 6.5.3 Vital signs

Vital signs include blood pressure (BP) and heart rate measurements. After the subject has been sitting for 3-5 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using an automated validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. At screening and baseline, vital signs will also be assessed again after three minutes in the standing position.

If vital signs at screening and baseline are out-of-(appropriate)range, taking into consideration the health-status of the patient, the Investigator should obtain two additional readings**,** so that a total of up to three consecutive assessments are made, with the subject seated quietly for approximately five minutes preceding each repeat assessment.

### 6.5.4 Height, weight, and body temperature

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

Body mass index (BMI) will be calculated using the following formula:

- BMI = Body weight (kg) / [Height (m)]$^2$

Body temperature will be captured in °C.

### 6.5.5 Laboratory evaluations

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a **protocol-specified range** at screening and/or at the initial baseline, the assessment may be repeated prior to randomization. If the repeat value remains outside of protocol-specified ranges, the subject should be excluded from the study.

In the case where a laboratory range is **not specified by the protocol**, but is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated prior to randomization.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to continue in the study.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated

evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

#### 6.5.5.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (e.g. neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count will be measured.

During the follow-up visits starting from Week 76, immunoglobulin and immunoglobulin subsets (IgG, IgM, IgA and IgE) will be measured.

#### 6.5.5.2 Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/$CO_2$, calcium, cholesterol, chloride, creatinine, CK, γ-GT, glucose, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, urea or BUN and uric acid.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

#### 6.5.5.3 Urinalysis

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

A semi-quantitative "dipstick" evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood.

If the dipstick result is positive for protein, nitrite, leucocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.

### 6.5.6 Electrocardiogram (ECG)

Standard 12 lead ECGs will be collected at the time points specified in the Assessment schedule.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG / in the ECG section of the CRF. Each ECG tracing should be labeled with the

- study number
- subject / patient initials
- subject / patient number
- date

and kept in the source documents at the study site. Clinically significant abnormalities should be recorded on the relevant medical history/Current medical conditions CRF page prior to informed consent signature and on the Adverse Events page thereafter. Clinically significant findings must be discussed with the sponsor.

The CRF will contain:

- date and time of ECG
- heart rate
- PR interval
- QT interval
- QRS duration

Original ECG tracings, appropriately signed, will be archived at study site.

### 6.5.7 Pregnancy

Pregnancy tests are required of all female subjects regardless of reported reproductive/menopausal status.

Serum pregnancy tests will be performed at screening; at all other times urine pregnancy tests may be used. The screening pregnancy test result must be received before the subject may be dosed.

Urine pregnancy will be performed at Baseline (Day 1) and every post-dose visit from Week 3 onwards, and may be conducted in addition at the discretion of the investigator or may be required more frequently by local practices, if a menstrual cycle is missed, or if potential pregnancy is otherwise suspected.

If a urine pregnancy test is performed and is found to be positive, the subject must be discontinued from the trial.

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## 6.6 Pharmacokinetic assessments

See Assessment schedule table, and sample log table in Section 13-Appendix 1.

### 6.6.1 PK Blood collection and processing

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Two (2) mL of blood will be collected into plain barrier (Serum Separator) tubes (no anti-coagulant) to obtain approximately 1 mL serum. For a detailed description of blood sampling schema, please refer to the Blood Log in Section 13-Appendix 1.

### 6.6.2 Urine collection and processing

Not applicable.

### 6.6.3 Pharmacokinetic analytical method(s)

A validated enzyme-linked immunoassay (ELISA) will be used to determine VAY736 serum concentrations in the clinical trial subjects. Commercially Confidential Information

### 6.6.4 Pharmacokinetic parameters

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

The following pharmacokinetic parameters of VAY736 will be determined using the actual recorded sampling times and non-compartmental method(s) with WinNonlin Phoenix (Version 6.2 or higher): from the plasma concentration-time data.

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With regards to the limited sampling design, it is anticipated that clearance, volume of distribution could not be derived using non-compartmental method. They will be determined using modeling approach, as appropriate.

## 6.7 Other Assessments

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### 6.7.5 Skin Biopsy

Biopsies with a minimum diameter of 4 mm will be taken at the timepoints outlined in the Assessment Schedule and will be used as indicated for histology or direct immunofluorescence. Skin biopsies for diagnosis purpose to cover inclusion criteria #3 (if results) not already available will be taken from lesional (histology) and perilesional (direct immunofluorescence) skin. All skin biopsies will be taken by trained site staff experienced in conducting the procedure. Appropriate local anesthetic will be provided and the procedure will be performed in compliance with local guidelines and standards of practice.

The actual sample collection date and time will be entered in the (e)CRF.

Details of sample processing, handling, storage, and shipment will be provided in a separate laboratory manual.

### 6.7.6 Digital photography

Regional photographs (e.g. torso, extremities, mouth) and close-up photographs of selected areas with active disease will be taken at some study visits (see Assessment schedule). The patient may define what areas may be serially photographed throughout the study duration in instances where the patient is sensitive to being photographed. This is acceptable so long as photographs adequately convey disease activity based on the Investigator's judgment.

All efforts should be made to keep the photographs standardized as much as possible, including focus, shutter, aperture, distance, background, flash, filters, lenses and potential tripod use.

Additional guidance will be provided in a separate manual.

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# 7 Safety monitoring

## 7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., 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. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. Pre-existing medical conditions/diseases (i.e. Medical History(ies)) are considered AEs if they worsen after providing written informed consent. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, or are considered clinically significant, or they require therapy.

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

All adverse events will be reported from the time the subject has provided informed consent to visit 14 (week 52). Starting from Week 76 (visit 15) until end of study, only AEs related to VAY736 and/or infection, potential malignant events and neutropenia will be recorded (only valid for AEs, not for SAEs).

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

1. the severity grade
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. its relationship to study treatment
3. its duration (e.g. start and end date)
4. whether it constitutes a serious adverse event (SAE)
5. action taken regarding study treatment
6. whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
7. its outcome

An SAE is defined as any AE 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
  - 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 form
  - 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 subject's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

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

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see **Section 7.2**

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should 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 Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the informed consent and should be discussed with the subject during the study as needed.

## 7.2 Serious adverse event reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the subject has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is the later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after End of Study must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow-up information) is collected and recorded in English on the paper Serious Adverse Event Report Form or the electronic Serious Adverse Event Form within the OC/RDC system (where available). The Investigator must assess the relationship to each specific component of the study treatment (if the study treatment consists of several components).

SAEs (initial and follow-up) that are recorded *on the paper SAE form* should be faxed within 24 hours of awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department and also a copy to the Novartis Translational Medical Expert and/or Clinical Trial Leader (according to page 2). The telephone and fax numbers of the contact persons in the local Drug Safety and Epidemiology department, specific to the site, are listed on page 2 of this protocol and/or in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

SAEs (initial and follow-up) that are recorded *electronically* in the OC/RDC system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first. Study site personnel must also inform the Novartis Translational Medical Expert and/or Clinical Trial Leader (according to page 2).

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

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 investigational 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 investigational 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 Directive 2001/20/EC 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.

Liver events are divided into two categories:

- Liver events of special interest (AESI) which consist of LFTs elevations
- Medically significant liver events which are considered as serious adverse events (SAEs) and which consist of marked elevations of LFTs and / or pre-specified adverse events.

Please refer to Table 15-1-Appendix 3 for complete definitions of liver events.

Any liver event which meets the criteria for a "**medically significant**" event should follow the **standard procedures for SAE reporting** as described in Section 7.2.

Every liver event as defined in Table 15-1-Appendix 3 should be followed up by the investigator or designated personal at the trial site, as summarized below and detailed in Table 15-2-Appendix 3.

- 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 should be recorded as appropriate in the CRF.

## 7.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring while the patient is on study treatment 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 should be recorded on a Clinical Trial 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 investigational treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

## 7.5 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

# 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 CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each subject 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 subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

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 the recording of data that will be used for all primary and safety 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 subjects will be disclosed.

## 8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the

data to the CRO working on behalf of Novartis. 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 a CD-ROM or paper copies of the subject data for archiving at the investigational site.

All data captured for this study will have an external originating source (either written or electronic), the CRF is not considered as source.

## 8.3 Database management and quality control

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

The CRO working on behalf of Novartis review the data entered into the eCRFs 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. If the electronic query system is not used, a paper Data Query Form will be sent (e.g. fax, e-mail) to the site. Site personnel will complete and sign the copy, then send it (with original signature) back to Novartis staff who will make the correction to the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Standard blood safety laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

At the conclusion of a non-IRT study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis. The occurrence of any 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 by joint written agreement between the Global Head of Clinical Information Sciences and the Clinical Franchise Head.

## 8.4 Safety Data Review Committee

An internal Safety Data Monitoring Committee (DMC) will be established to review safety data in an unblinded fashion throughout the conduct of the study. Specific details of the composition and scope of its mandate will be presented in a DMC charter document. The committee will be comprised of study-independent physician(s), clinical researchers and a statistician. The DMC members will be separate from the pre-clinical and clinical teams involved in the VAY736 program. Full details of the committee's mandate will be provided in the team charter, but at a minimum the Safety DMC will make recommendations concerning study continuation and/or material changes in the risk/benefit profile of VAY736 in PV patients to the study team. The Safety DMC will review all safety data available to the 9$^{th}$ patient achieving Week 6, the "safety review" milestone of the study design. The Safety DMC will review all safety data available after the 14$^{th}$ patient completes week 12 (this review will include data from patients on 10 mg/kg VAY736), The Safety DMC will also review every documented SUSAR.

## 8.5 Adjudication Committee

Not required.

# 9 Data analysis

## 9.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The full analysis set will include all subjects that received any study drug.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with available PK data and no protocol deviations with relevant impact on PK data.

The primary PK analysis set will include all subjects with available PK data. The secondary PK analysis set will include all subjects with available PK data and no protocol deviations with relevant impact on PK data.

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## 9.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

## 9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject.

## 9.4 Analysis of the primary variable(s)

The primary aim of this study is to compare the efficacy of a single i.v. dose of VAY736 in reducing the clinical disease activity of pemphigus vulgaris patients as determined by the change in Pemphigus Disease Area Index (PDAI) between baseline and week 12. The statistical analysis model will include data on the PDAI from all timepoints at which it was recorded (baseline, weeks 3, 6, 8, 12, 16, 20 and 24) but the primary comparison is made for week 12.

### 9.4.1 Variable(s)

The primary efficacy variable is the PDAI skin and mucous membranes activity score (i.e. the sum of the skin activity sub-score and mucous membranes activity sub-score of the PDAI) recorded at baseline and weeks 3, 6, 9, 12, 16, 20 and 24.

### 9.4.2 Statistical model, hypothesis, and method of analysis

It is assumed that the PDAI skin and mucous membranes activity score will follow an approximate normal distribution. If, on blinded review of the data, this assumption appears to not be met, alternative statistical methods may be applied. These will be described full in the Reporting and Analysis Plan (RAP).

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### 9.4.3 Handling of missing values/censoring/discontinuations

Patients with missing PDAI at baseline will not be included in the analysis. Patients with missing data at one or more timepoints post baseline will be included in the analysis. The planned 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.

### 9.4.4 Supportive analyses

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## 9.5 Analysis of secondary Commercially Confidential Information variables

Secondary efficacy variables supporting the secondary objectives are:

- PDAI total score recorded at baseline and weeks 3, 6, 9, 12, 16, 20 and 24.
- ABSIS recorded at baseline and weeks 3, 6, 9, 12, 16, 20 and 24.
- Proportion of patients experiencing control of disease activity at weeks 1, 3, 6, 9, 12, 20 and 24.
- IGA recorded at baseline and weeks 3, 6, 9, 12, 16, 20 and 24.

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### 9.5.1 Efficacy / Pharmacodynamics

The secondary efficacy variables will be analyzed as follows:

The PDAI total score, ABSIS score will be analyzed following the same approach used for the primary efficacy variable.

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The number and percentage of patients in each category of response for the IGA will be presented for each week.

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### 9.5.2 Safety

#### Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

#### ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

#### Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

#### Adverse events

All information obtained on adverse events will be displayed by treatment and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

### 9.5.3 Pharmacokinetics

VAY736 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point,

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Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

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Pharmacokinetic parameters will be calculated as described in Section 6.6.3 and will be listed by treatment and subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

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## 9.6 Sample size calculation

With 9 patients treated with VAY736 and 6 with placebo in the analysis of the primary efficacy variable, the study would have less than 1% chance of having a false-positive result, i.e. of meeting both the efficacy criteria when the true difference between VAY736 and placebo is zero. Additionally the chances of meeting both the efficacy criteria remain below 20% for true differences between VAY736 and placebo of less than 6 points.

The study would have approximately 80% chance of meeting both the efficacy criteria, when the true difference between VAY736 and placebo is 14 points.

These calculations assume that the primary efficacy variable, follows a normal distribution with a standard deviation of 8. This estimate of the standard deviation is based on a study assessing the reliability of the PDAI (Rosenbach et al 2009).

## 9.7 Power for analysis of key secondary variables

Not applicable

## 9.8 Interim analyses

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# 10 Ethical considerations

## 10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented 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 Code of Federal Regulations Title 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 subjects 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 of the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should 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 (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject 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 should be informed that taking the study drug 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 subject will not reliably comply, they should not be entered in the study.

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In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

## 10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. 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 Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, 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

Novartis assures that 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.

# 11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the 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/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

## 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/REB. Only amendments that are required for subject safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the Health Authorities (where required) and the IRB/IEC/REB at the study site should be informed within 10 working days or less, if required by local regulation.

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Available upon request.

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# 13 Appendix 1: Sample Log table – all matrices

# 14 Appendix 2: Sample labeling and shipping information

This information will be provided in a separate manual.

# 15 Appendix 3: Liver event definitions and follow-up requirements

**Table 15-1 Liver Event Definitions**

| | **Definition/ threshold** |
|---|---|
| **Adverse event of special interest** | |
| Laboratory values | ALT or AST > 3 x ULN |
| | ALP > 2 x ULN |
| | TBL > 1.5 x ULN |
| **Medically significant event (SAE)** | |
| Laboratory values | ALT or AST > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction]) |
| | ALP > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction]) |
| | TBL > 3 x ULN |
| | Potential Hy's Law cases (defined as ALT/AST > 3 x ULN and TBL > 2 x ULN [mainly conjugated fraction] without notable increase in ALP to > 2 x ULN) |
| Adverse events | Any clinical event of jaundice (or equivalent term) |
| | ALT or AST > 3 x ULN accompanied by general malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia |
| | Any event that links to a preferred term (PT) in the MedDRA dictionary falling under the SMQ sub-module "Drug-related hepatic disorders – severe events only"* or any "Hy's law case" PT |

* 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

**Table 15-2 Liver Event Follow Up Requirements**

| Criteria | Event type | Actions required | Follow-up monitoring |
|---|---|---|---|
| Potential Hy's Law case[a] | Medically significant | Hospitalize, if clinically appropriate<br>Report to Novartis as an SAE<br>Establish causality | ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| **ALT or AST** | | | |
| > 8 x ULN | Medically significant | Repeat LFT within 48 hours<br>Hospitalize if clinically appropriate<br>Report to Novartis as an SAE<br>Establish causality | ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| > 5 to ≤ 8 x ULN | Medically significant | Repeat LFT within 48 hours<br>Report to Novartis as an SAE<br>Establish causality | ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| > 3 x ULN accompanied by symptoms[b] | Medically significant | Hospitalize if clinically appropriate<br>Report to Novartis as an SAE<br>Establish causality | ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| > 3 to ≤ 5 x ULN<br>(patient is asymptomatic) | AESI | Central laboratory to report to Investigator & Novartis<br>Repeat LFT once or twice in the week<br>If elevation persists, establish causality | Investigator discretion<br>Monitor LFT within 1 to 4 weeks or at next visit |
| ≤ 3 x ULN<br>(patient is asymptomatic) | N/A | Repeat LFT at next visit | |
| **ALP (isolated)** | | | |
| > 5 x ULN | Medically significant | Repeat LFT within 48 hours<br>If elevation persists, report to Novartis as an SAE<br>Establish causality | Investigator discretion<br>Monitor LFT within 1 to 4 weeks or at next visit |
| > 2 to ≤5 x ULN<br>(patient is asymptomatic) | AESI | Central laboratory to report to Investigator & Novartis<br>Repeat LFT once or twice in the week<br>If elevation persists, establish causality | Investigator discretion<br>Monitor LFT within 1 to 4 weeks or at next visit |
| ≤ 2 x ULN<br>(patient is asymptomatic) | N/A | Repeat LFT at next visit | |

| Criteria | Event type | Actions required | Follow-up monitoring |
|---|---|---|---|
| **TBL (isolated)** | | | |
| > 3 x ULN | Medically significant | Repeat LFT within 48 hours<br>Hospitalize if clinically appropriate<br>Report to Novartis as an SAE<br>Establish causality | ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)<br>Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin) |
| > 1.5 to ≤ 3 x ULN<br>(patient is asymptomatic) | AESI | Central laboratory to report to Novartis<br>Repeat LFT once or twice in the week<br>If elevation persists, establish causality | investigator discretion<br>Monitor LFT within 1 to 4 weeks or at next visit |
| ≤ 1.5 x ULN<br>(patient is asymptomatic) | N/A | Repeat LFT at next visit | |
| **Preferred terms** | | | |
| Jaundice | Medically significant | Hospitalize the patient<br>Report to Novartis as an SAE<br>Establish causality | ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| "Drug-related hepatic disorders - severe events only" SMQ AE | Medically significant | hospitalization if clinically appropriate<br>Report to Novartis as an SAE<br>Establish causality | Investigator discretion |

[a] Elevated ALT/AST > 3 x ULN and TBL > 2 x ULN but with no notable increase in ALP to > 2 x ULN

[b] General malaise, fatigue, abdominal pain, nausea, or vomiting, rash with eosinophilia

[c] Resolution is defined as an outcome of one of the following: return to baseline values, stable values at three subsequent monitoring visits at least 2 weeks apart, remain at elevated level after a maximum of 6 months, liver transplantation, and death.

# 16 Appendix 4: Blinding and unblinding

Randomization data are kept strictly confidential, and are accessible only to authorized personnel, until unblinding of the trial as described in the table below.

**Table 16-1 Blinding levels**

| Role | Time or Event | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Drug Supply | UI | UI | UI | UI | UI | UI | UI | UI | UI |
| Randomization Office | UI | UI | UI | UI | UI | UI | UI | UI | UI |
| Patient | B | B | B | UI | UI | B | B | UI | UI |
| Treating Physician | B | B | B | UI | UI | B | B | UI | UI |
| Primary Investigator | B | B | B | UI | UI | B | B | UI | UI |
| Unblinded Investigator (review of hematology) | B | B | B | UI | UI | UI | UI | UI | UI |
| Study Blinded Monitor | B | B | B | UI | UI | B | B | UI | UI |
| Study Unblinded Monitor | B | UI | UI | UI | UI | UI | UI | UI | UI |
| Clinical Trial Leader | B | B | B | UI | UI | B | UG | UI | UI |
| Data Manager | B | B | B | UI | UI | B | B | B | UI |
| PK Bioanalytics | B | UI | UI | UI | UI | UI | UI | UI | UI |
| PK Expert | B | B | B | UI | UI | B | UG | UI | UI |
| Statistician | B | B | B | UI | UI | B | UI | UI | UI |
| Translational Medicine Expert | B | B | B | UI | UI | B | UG | UI | UI |
| Modeler | B | B | B | UI | UI | B | UI | UI | UI |
| Programmer | B | B | B | UI | UI | B | UI | UI | UI |
| Novartis decision team | B | B | B | UI | B | B | UG | UI | UI |
| Data Review Committee | B | B | B | UI | UI | UI | B | B | UI |

UG Allowed to be unblinded on treatment group level

UI Allowed to be unblinded on individual patient level

B Remains blinded

1 Generation of randomization list, QC and lock randomization list

2 Patient allocation to treatment

3 Treatment administration

4 Safety emergency event (unblinding of a single subject)

5 Unblinding of a single patient after Week 24 (or Week 12 for early withdrawal that meets certain conditions see Section 5.5.8)

6 DMC Safety review (9$^{th}$ patients included in the analysis has completed Week 6)

7 Interim analysis not for DMC (some patients included in the analysis have not yet completed the study)

8 Interim analysis not for DMC review (all patients included in the analysis have completed the study)

9 Database lock or after all patients have been unblinded

The bioanalyst will receive a copy of the randomization schedule to facilitate analysis of the pharmacokinetic samples. The bioanalyst may provide concentration data to the PK expert under blinded conditions and will keep unblinding information confidential until final clinical database lock.

# 17 Appendix 5: Decision tree following unblinding at Week 24

# 18 Appendix 6: Pemphigus Disease Area Index Scoring Sheet

**Pemphigus Disease Area Index (PDAI)**

| Skin | Activity | | Damage |
|---|---|---|---|
| Anatomical location | Erosion/Blisters or new erythema | | Post-inflammatory hyperpigmentation or erythema from resolving lesion |
| | 0 absent<br>1 1 lesion, up to one >2 cm in any diameter, none >6 cm<br>1.3 2 lesions, up to one >2 cm in any diameter, none >6 cm<br>1.6 3 lesions, up to one >2 cm in any diameter, none >6 cm<br>2 2-3 lesions, at least two >2 cm diameter, none >6 cm<br>3 >3 lesions, none >6 cm diameter<br>5 >3 lesions, and/or at least one >6 cm diameter<br>10 >3 lesions, and/or at least one lesion >16 cm diameter or entire area | Number lesions if ≤3 | 0 absent<br>1 present |
| Ears | | | |
| Nose | | | |
| Rest of the face | | | |
| Neck | | | |
| Chest | | | |
| Abdomen | | | |
| Back, buttocks | | | |
| Arms | | | |
| Hands | | | |
| Legs | | | |
| Feet | | | |
| Genitals | | | |
| **Total Skin** | /120 | | /12 |

**Scalp**

| Scalp | Erosion/Blisters or new erythema | Number lesions if ≤3 | Post-inflammatory hyperpigmentation or erythema from resolving lesion |
|---|---|---|---|
| | 0 absent<br>1 in one quadrant<br>2 two quadrants<br>3 three quadrants<br>4 affects whole skull<br>10 at least one lesion >6 cm | | 0 absent<br>1 present |
| **Total Scalp** | /10 | | /1 |

**Mucous membrane**

| Anatomical location | Erosion/Blisters | |
|---|---|---|
| | 0 absent<br>1 1 lesions<br>2 2-3 lesions<br>5 >3 lesions or 2 lesions >2 cm<br>10 entire area | Number lesions if ≤3 |
| Eyes | | |
| Nose | | |
| Buccal mucosa | | |
| Hard palate | | |
| Soft palate | | |
| Upper gingiva | | |
| Lower gingiva | | |
| Tongue | | |
| Floor of mouth | | |
| Labial bucosa | | |
| Posterior pharynx | | |
| Anogenital | | |
| **Total Mucosa** | /120 | |

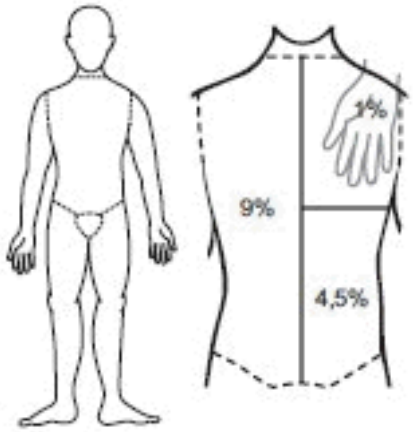
**Total Activity Score**
= Total Skin Activity Score + Total Scalp Activity Score + Total Mucosa Activity Score

**Total Damage Score**
= Total Skin Damage Score + Total Scalp Damage Score

## PDAI Score

**= Total Activity Score + Total Damage Score**

# 19 Appendix 7: Assessment of Body Surface Area




| | | | |
|---|---|---|---|
| Head & neck: | 9% | Arm incl hand: | 9% |
| Trunk (front & back) | 36% | Leg: | 18% |
| Genitals: | 1% | Palm of the hand (including fingers): | 1% |

# 20 Appendix 8: ABSIS scoring sheet

ABSIS SCORING SHEET

Date:_____
Patient`s weight (kg):_____

| Skin Involvement (Max BSA) | Patient`s BSA | Weighting Factor | % BSA x Weighting Factor |
|---|---|---|---|
| Head & neck (9%) | | | |
| L Arm including hand (9%) | | | |
| R Arm including hand (9%) | | | |
| Trunk (front & back) (36%) | | | |
| L Leg (18%) | | | |
| R Leg (18%) | | | |
| Genitals (1%) | | | |
| | | | Total Score[1]_____ |

[1]*Skin Involvement Total Score ranges from 0 – 150 points*

| Legend for weighting factor (most dominant appearance of skin lesions): | |
|---|---|
| 1.5 | Erosive, exudative lesions |
| 1.0 | Erosive, dry lesions |
| 0.5 | Reepithelialized lesions (incl. post inflammatory erythema and/or hyperpigmentation) |

I. Oral Extent (enter 1 for presence of lesions, 0 absence of any lesion):

| | |
|---|---|
| Upper gingival mucosa | |
| Lower gingival mucosa | |
| Upper lip mucosa | |
| Lower lip mucosa | |
| Left buccal mucosa | |
| Right buccal mucosa | |
| Tongue | |
| Floor of the mouth | |
| Hard palate | |
| Soft palate | |
| Pharynx | |
| | Total Score[2]_____ |

[2]*Oral Total Score ranges from 0-11*

II. **Severity** (Subject discomfort during eating/drinking)

| Food, e.g. | Level | Factor of Discomfort | Level x Factor of Discomfort |
|---|---|---|---|
| Water | 1 | | |
| Soup | 2 | | |
| Yogurt | 3 | | |
| Custard | 4 | | |
| Mashed potatoes/scrambled egg | 5 | | |
| Baked fish | 6 | | |
| White bread | 7 | | |
| Apple/ raw carrot | 8 | | |
| Fried steak/ whole-grain bread | 9 | | |
| | | | Total Score[3]_____ |

[3] *Total Severity Score ranges from 0-45*

| Legend for Factor of Discomfort | |
|---|---|
| 1 | Pain/bleeding occurred always |
| 0.5 | Pain/bleeding occurred sometimes |
| 0 | Never experienced problems |

***ABSIS Score***

***= Total Skin Involvement Score + Total Oral Score + Total Severity Score (Food)***

# 21 Appendix 9: IGA Scale

| Score | | | | Cutaneous disease | Mucosal disease |
|---|---|---|---|---|---|
| ❑ | 0 | = | Clear | No signs of active PV disease | No signs of active PV disease |
| ❑ | 1 | = | Almost clear | <1% BSA affected by active PV lesions | Some erosions, but no difficulty in swallowing or chewing |
| ❑ | 2 | = | Mild | 1 to <3% BSA affected by active PV lesions | Buccal and gingivolabial mucosal involvement.<br>Difficulty for solid food intake. |
| ❑ | 3 | = | Moderate | 3 to 10% BSA affected by active PV lesions | Extensive oral mucosal involvement. Difficulty for semisolid food intake. |
| ❑ | 4 | = | Severe | >10% BSA affected by active PV lesions | Extensive oral mucosal involvement with other mucous membranes involved. Difficulty in swallowing liquids and any other food. |