Statistical Analysis Plan

for Final Analysis

Protocol No. MT-2766-A-101 (CP-PRO-CoVLP-028)

A Phase I/II, Randomized, Placebo-Controlled Study to Evaluate the Safety and Immunogenicity of MT-2766 in Japanese Adults

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APPROVAL FORM

Statistical Analysis Plan

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ABBREVIATIONS

Abbreviations	Definitions
AE	adverse event
ALT	alanine transaminase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BDR	blinded data review
BLQ	below limit of quantification
BMI	body mass index
CI	confidence interval
CV	coefficient of variation
DP	decimal places
DMC	data monitoring committee
ECG	electrocardiogram
FAS	full analysis set
ITT	intent-to-treat
LLOQ	lower limit of quantitation
MedDRA	medical dictionary for regulatory activities
MMRM	mixed model repeated measures
PD	pharmacodynamics
PDPOP	PD Population
PK	pharmacokinetics
PKPOP	PK Population
PP	per protocol
PT	preferred term
RAND	all subjects randomized population
SAP	statistical analysis plan
SAE	serious adverse event
SAF	safety population
SD	standard deviation
SOC	system organ class
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse events
ULN	upper limit of normal range
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) is based on the final protocol (v3.0) dated 16-NOV-2021. The plan covers statistical analysis, tabulations and listings of the study data to assess the safety and immunogenicity of MT-2766.

Any statistical analysis details described in this document supersede any description of statistical analysis in the protocol.

2 STUDY OBJECTIVE AND ENDPOINTS

2.1 Study Objective(s)

The objective of this study is to evaluate the safety and immunogenicity of MT-2766 in Japanese adults.

2.2 Study Endpoint(s)

2.2.1 Primary Endpoints

The following primary immunogenicity and safety endpoints are for Groups 1 (3.75 μg of MT-2766) and Group 2 (placebo for MT-2766 3.75 μg).

Safety:

1. The incidences, severity, and investigator-assessed causality of immediate adverse events (AEs) that occur within 30 minutes of first (Day 0) and second (Day 21) injections.
2. The incidences and severity of the following solicited AEs that develop within 7 days of first (Day 0) and second (Day 21) injections: (i) local AEs (injection site erythema, injection site swelling, injection site induration, and injection site pain) and (ii) systemic AEs (fever, headache, fatigue, muscle aches, joint aches, chills, a feeling of general discomfort, swelling in the axilla, and swelling in the neck).
3. The incidences, severity, and investigator-assessed causality of unsolicited AEs that develop within 21 days of first (Day 0) and second (Day 21) injections.
4. The incidences of serious AEs (SAEs), medically attended AEs (MAAEs), AEs leading to withdrawal, AEs of special interest (AESIs), and deaths up to 21 days following first (Day 0) and second (Day 21) injections. AESIs include vaccine-associated enhanced diseases (VAED), hypersensitivity reactions, and potential immune-mediated diseases (pIMDs).

Immunogenicity:

1. SARS-CoV-2 neutralizing antibody (Nab) responses will be analyzed on Days 0, 21, and 42 using the following parameters: geometric mean antibody titer (GMT), seroconversion (SC) rate, and geometric mean fold rise (GMFR);
2. SARS-CoV-2-specific T helper 1 (Th1) cell-mediated immune (CMI) responses will be measured on Days 0, 21, and 42 using the interferon (IFN)-γ enzyme-linked immunospot (ELISpot) assay;
3. SARS-CoV-2-specific T helper 2 (Th2) CMI responses will be measured on Days 0, 21, and 42 using the interleukin (IL)-4 ELISpot assay.

2.2.2 Secondary Endpoints

The following secondary safety and immunogenicity endpoints are for Groups 1 and Group 2.

Safety:

1. The incidences of SAEs, MAAEs, AEs leading to withdrawal, AESIs, and deaths from Day 43 to Day 201;
2. The incidences of SAEs, MAAEs, AEs leading to withdrawal, AESIs, and deaths from Day 202 to Day 386;
3. The numbers and percentages of subjects with normal and abnormal urine, hematological, and biochemical test results within three days of first (Day 0) and second (Day 21) injections.

Immunogenicity:

1. Persistence of SARS-CoV-2 Nab response will be assessed on Days 128, 201, and 386 using the following parameters: GMT, SC rate, and GMFR.
2. SARS-CoV-2-specific antibody responses will be measured on Days 0, 21, and 42 based on the total immunoglobulin G (IgG) level, and the persistence of these antibodies will be analyzed on Days 128, 201, and 386 using the following parameters: GMT, SC rate, and GMFR;
3. SARS-CoV-2-specific Th1 CMI responses will be measured on Days 201 and 386 using the IFN-γ ELISpot assay;
4. SARS-CoV-2-specific Th2 CMI responses will be measured on Days 201 and 386 using the IL-4 ELISpot assay;

2.2.3 Exploratory Endpoints

Immunogenicity:

1. For Group 1 and Group 2, SARS-CoV-2-specific CMI responses will be assessed on Days 0, 21, 42, 201, and 386 based on the percentage of CD4+ T cells expressing functional markers.
2. For Group 1 and Group 2, plant glycan–specific antibody responses will be assessed on Days 0, 42, 201 and 386 based on serum IgE levels directed against bromelain-derived cross-reactive carbohydrate determinant MUXF3.
3. For Group 1 and Group 2, Further characterization of the MT-2766–induced immune response, if informative;
4. For Group 3 (1.875 μg of MT-2766), the same analyses as the primary and secondary endpoints in Groups 1 and Group 2 will be performed as exploratory endpoints.

Safety

1. For Group 3, the same analyses as the primary and secondary endpoints in Groups 1 and Group 2 will be performed as exploratory endpoints.

3 STUDY DESIGN

3.1 Study Phase

Study phase: Phase I/II

3.2 Study Design

A randomized, multicenter, observer-blinded, placebo-controlled study with Japanese male and female subjects who are seronegative for SARS-COV-2 antibodies and negative for SARS-COV-2 PCR test at screening.

125 subjects will be randomized 4:1 and will receive the same 3.75 μg of MT-2766 or placebo. Subjects will receive two intramuscular (IM) injections 21 days apart on Days 0 and 21, into the deltoid region of the alternating arm (each arm will be injected once), of one of the following blinded treatments:

- Group 1: 3.75 μg of MT-2766 in a final volume of 0.5 mL (n=100)
- Group 2: Placebo for MT-2766 3.75 μg in a final volume of 0.5 mL (n=25)

In addition, subjects in Group 3 (n=20) will receive two IM injections of 1.875 μg MT-2766 21 days apart on Days 0 and 21, into the deltoid region of the alternating arm (each arm will be injected once) under open-label. The study may be completed even if fewer than 20 subjects in Group 3 are enrolled.

- Group 3: 1.875 μg of MT-2766 in a final volume of 0.25 mL (n=20)

Subjects will be screened up to 21 days in advance of the first vaccine administration and will demonstrate a satisfactory baseline medical assessment by history, general physical examination, hematological, biochemical, urinalysis and serological analysis. Although tests for SARS-CoV-2 antibodies and PCR will be performed at screening, negative subjects will be enrolled. On Day 0 and Day 21, vaccine administration will occur. Phone contacts will be made after each vaccine administration, specifically for review of the subject's safety and concomitant medication data. Visits to the study site will occur 3 days after each vaccine administration for key safety assessments, and 21 days after each vaccine administration for key safety and immunogenicity assessments.

Subjects will return to the study site on Day 128, Day 201, and Day 386 (3-month, 6-month, and 12-month safety follow-ups and immunogenicity assessments after the last vaccine administration).

In Group 1 and Group 2, the randomization code will be opened after data lock when all subjects in Groups 1 and 2 have reached Day 42. Once the study is unblinded, if the efficacy may be inadequate or unconfirmable, public vaccination will be allowed in Group 1 (3.75 μg of MT-2766). Once the study is unblinded, public vaccination will be allowed in Group 2 (placebo group). In these cases the subject will be withdrawn from the study.

In Group 3, if the efficacy may be inadequate or unconfirmable, public vaccination will be recommended. In this case the subject will be withdrawn from the study.

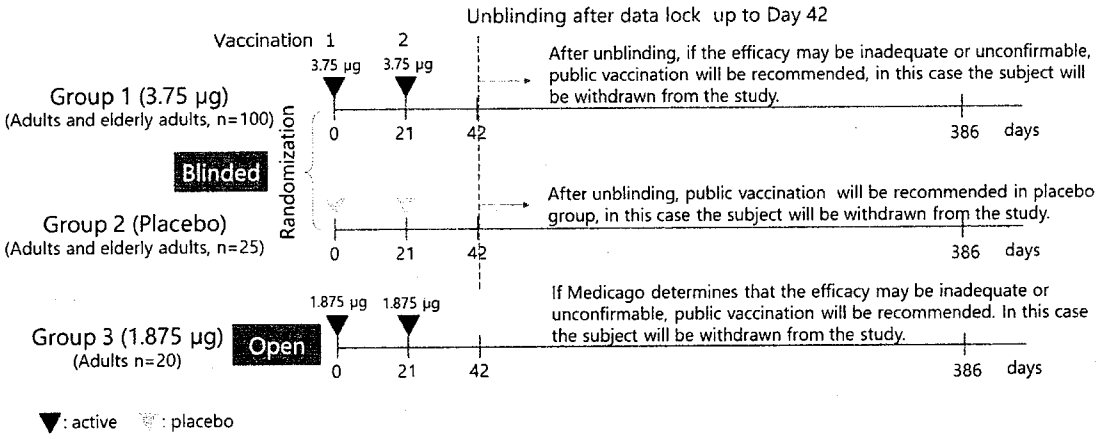

Figure 1 Study Flow

3.3 Schedule for Tests and Observations

Table 1 shows the parameters of tests and observation, and the schedule.

Table 1 Time and Events Schedule

	Days −21 to Day −1 (screening)	Day 0		Day 1 (+1)	Day 3 (±1)	Day 8 (±1)	Day 15 (±1)	Day 21 (±2)[13]		Day 22 (±1)	Day 24 (±1)	Day 29 (±2)	Day 36 (±2)	Day 42 (±2)	Day49 (±2)
Visit Number	1	2		Phone[12]	3	Phone[12]	Phone[12]	4		Phone[12]	5	Phone[12]	Phone[12]	6	Phone[12]
		Before vaccination	After vaccination					Before vaccination	After vaccination						
Informed consent	X														
Demographics	X														
Medical history /Complications	X	X													
Prior medication	X	X													
Inclusion/Exclusion criteria	X	X													
Randomization (for Groups 1&2)		X													
Vaccine administration		X						X							
Physical examination	X	X	X		X			X	X		X			X	
Vital signs [1]	X	X	X		X			X	X		X			X	
Height(screening only)/Weight/BMI	X	X													
SARS-CoV-2 PCR test	X														
SARS-CoV-2 antibody test [2]	X														
Blood chemistry [3] /Hematology [4]	X	X			X			X			X			X	
Urinalysis[5]	X	X			X			X			X			X	
HIV/HBV/HCV	X														
Pregnancy test [6]	X[5]	X						X						X	
Immunogenicity -Serology (Nab assay/ ELISA/ anti-plant glycans IgE antibodies) [7]		X						X						X	
Immunogenicity - CMI response ((ELISpot and ICS) [8]		X						X						X	
Immediate surveillance			X						X						
Provide and collect paper diary and memory aid [9]			X		X			X			X			X	
Collection of solicited local/systemic AEs			X	X	X	X			X	X	X	X			
Concomitant medications [10]			←												→
AEs, SAEs, AESIs, MAAEs [11]			←												→
Collection of COVID-19 symptoms			Subjects will be instructed to contact the study site if they experience symptoms of COVID-19 from the day of the first vaccination (Day 0, post vaccination) until the end of the study.												

	Day 77 (±14)	Day 105 (±14)	Day 128[14] (±14)	Day 161 (±14)	Day 189 (±14)	Day 201 (±14)	Day 245 (±14)	Day 273 (±14)	Day 301 (±14)	Day 329 (±14)	Day 357 (±14)	Day 386 (±14)
Visit Number	**Phone[12]**	**Phone[12]**	**7**	**Phone[12]**	**Phone[12]**	**8**	**Phone[12]**	**Phone[12]**	**Phone[12]**	**Phone[12]**	**Phone[12]**	**9**
Informed consent												
Demographics												
Medical history /Complications												
Prior medication												
Inclusion/Exclusion criteria												
Randomization												
Vaccine administration												
Physical examination			X			X						X
Vital signs [1]			X			X						X
Height(screening only)/Weight/BMI												
SARS-CoV-2 PCR test												
SARS-CoV-2 antibody test[2]						X						X
Blood chemistry [3] /Hematology [4]												
Urinalysis [5]												
HIV/HBV/HCV												
Pregnancy test [6]			X									
Immunogenicity -Serology (Nab assay/ ELISA/ anti-plant glycans IgE antibodies) [7]			X			X						X
Immunogenicity - CMI Response ((ELISpot and ICS) [8]						X						X
Immediate surveillance												
Provide and collect paper diary and memory aid [9]			X			X						X
Collection of solicited local/systemic AEs												
Concomitant medications [10]	←											→
AEs, SAEs, AESIs, MAAEs [11]	←											→
Collection of COVID-19 symptoms	Subjects will be instructed to contact the study site if they experience symptoms of COVID-19 from the day of the first vaccination (Day 0, post vaccination) until the end of the study.											

1) Resting blood pressure (BP), pulse rate (PR), respiratory rate (RR), and body temperature.
2) Anti-N antibodies will be measured at screening, Days 201 and 386.
3) Biochemistry (serum): Sodium, Potassium, Urea, Creatinine, Glucose, Bilirubin (total), Albumin, Total protein, Alkaline phosphatase, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma glutamyl transferase (GGT), Cholesterol (total, HDL, LDL), Triglycerides, Chloride, Calcium, Phosphorus.

4) Hematology: Hemoglobin, Hematocrit, Red blood cells, Platelets, Mean platelet volume (MPV), Neutrophils, Mean cell hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Mean cell volume (MCV), White cell count (total, WBC), Lymphocytes, Monocytes, Eosinophils, Basophils
5) Urinalysis: Macroscopic examination (color, clarity), pH, Specific gravity, Glucose, Protein, Occult blood
6) It will be tested in serum at screening and in urine at Days 0, 21, 42, and 128.
7) On Days 21 and 128, the immunogenicity- serology blood sample will be collected for the Nab assay and ELISA only. Anti-plant glycan IgE antibodies will only be measured on Days 0, 42, 201 and 386.
8) Blood samples may not be collected for all subjects.
9) If subject cannot use electronic diary, paper diary and memory aid will be acceptable.
10) From Day 43, concomitant medication collection will be limited to those used to treat an SAE, medically attended adverse event (MAAE), AE leading to withdrawal, AEs of special interest (AESIs), or an AE that occurred before Day 42 and that is still being used afterwards (i.e. on-going use).
11) AEs will be collected up to Day 49; SAEs, MAAEs, AEs leading to withdrawal, and AESIs will be collected through to the end of the study.
12) The study site should contact the subject via the electronic diary, phone, fax or email.
13) All efforts will be done to have subjects returning on planned date for Day 21 activities. If for any reason the visit is done before or after this planned date, subsequent visits/procedures will be adjusted accordingly.
14) Any subject who withdraws the study will be asked to undergo Day 128 visit procedures within two weeks of withdrawal, if the subject agrees. If a subject is withdrawn from Day 1 to Day 29, solicited local/systemic AEs are including. If a subject is withdrawn from Day 1 to Day 49, unsolicited AEs are investigated. If deemed necessary by (sub)investigator, necessary tests such as biochemistry, hematology, or urinalysis will be performed.

3.4 Sample Size and Power Considerations

The sample size is not based on a formal statistical power calculation but was considered to be adequate to meet the objectives of the study.

4 PLANNED ANALYSIS

4.1 Interim Analysis

Interim analyses for immunogenicity and safety will be conducted by MTPC after interim database lock up to Day 42 data in Group 1 and Group 2.

4.2 Final Analysis

The database will be locked twice. One is the interim database lock for the above-mentioned interim analyses (see Section 4.1), and the other is the final database lock for the final analyses. The SAP will be finalized and signed off prior to each database lock. Final data analysis will be conducted after the final database lock.

5 ANALYSIS SET

The statistical analysis will be based on separate analysis sets, defined as follows:

Safety Analysis Set (SAS):	All subjects who received at least one dose of either the MT-2766 or placebo.
Immunogenicity Intent-to-treat (ITT) Set	All subjects who receive at least one dose of either the MT-2766 or placebo and who have at least 1 post-baseline Immunogenicity assessment.
Immunogenicity Per Protocol (PP) Set	Immunogenicity ITT set who do not have any major protocol violations, and who received either the MT-2766 or placebo. For the Day 21 analysis, this should include the subjects who received the first vaccine dose and had Day 0 and Day 21 immunogenicity sample collections. For the Day 42 analysis, this should include the subjects who received both vaccine doses and had Day 0 and Day 42 immunogenicity sample collections. For the Day 128 analysis, this should include the subjects who received both vaccine doses and had Day 0 and Day 128 immunogenicity sample collections. For the Day 201 analysis, this should include the subjects who received both vaccine doses and had Day 0 and Day 201 immunogenicity sample collections.

All safety analyses will be performed using the SAS. The analyses of all immunogenicity endpoints will be performed using the Immunogenicity PP set as the primary analysis population, and the immunogenicity ITT set, as a secondary analysis population.

6 STATISTICAL CONSIDERATIONS

6.1 Descriptive Statistics

Unless otherwise specified, continuous data will be summarized descriptively using the number in the analysis set (N), the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the treatment group and analysis population being presented, unless otherwise specified.

6.2 Statistical Tests

Unless otherwise specified, all formal statistical tests will be done at two-sided significance level of 0.05. Point estimates will be accompanied with two-sided 95% CIs where applicable.

7 DATA CONVENTIONS

7.1 Analysis Variable Definitions

7.1.1 Study Subjects

7.1.1.1 Demographic and Other Baseline Characteristics

BMI will be recalculated to1decimal place using the following formula:

BMI (kg/m^2) = weight at screening (kg) / {height at screening (m)}^{2}

Significant comorbidities will be defined as co-morbid conditions that puts them at higher risk for severe COVID-19 disease. These significant comorbidities include obesity, hypertension, type 1 or type 2 diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular diseases, chronic kidney diseases, or be immunocompromised persons (e.g., treatment-controlled HIV infection, organ transplant recipients, or patients receiving cancer chemotherapy).

7.1.1.2 Medical History

Medical history will be coded according to the MedDRA version 24.1.

7.1.1.3 Prior or Concomitant Medication

Medications will be coded according to the WHO Drug Dictionary (WHO-DD) Global B3 version Sep 2021.

(1) Prior Medication

Prior medication is any medication that was started prior to study vaccine date and ended before study vaccine date.

(2) Concomitant Medication

Concomitant medication is a medication that starts on or after vaccination date/time at Day 0 or starts before vaccination and is still on-going at the time of the study vaccine.

7.1.2 Immunogenicity assessments

7.1.2.1 Geometric Mean Titer (GMT)

Continuous immunogenicity endpoints will be logarithmically transformed with 10 as base for analysis. GMT point estimates and the corresponding two-sided 95% CI by treatment group will be calculated as the antilog of the mean and 95% CI of log transformed titer values.

7.1.2.2 Geometric Mean Fold Rise (GMFR)

GMFR will be defined as the geometric mean of the ratio of GMTs (Day 21/Day 0, Day 42/Day 0, Day 128/Day 0, Day 201/Day 0).

7.1.2.3 Seroconversion (SC) Rate

SC rate is defined as the proportion of subjects achieving SC in the analysis set i.e. subjects with:

- For subjects with detectable Nab/IgG titer at Day 0 (i.e. baseline Nab/IgG titer $\geqslant$10): a $\geq$ 4-fold increase in Nab/IgG titers between Day 0 and Day 21/42/128/201, respectively.
- For subjects with undetectable Nab/IgG titer at Day 0 (i.e. baseline Nab/IgG titer < 10): Nab/IgG titer of $\geq$ 40 on Day 21/42/128/201, respectively.

7.1.2.4 Immunogenicity values

If antibody titers and concentrations are below the cutoff, i.e the result is of the form '<xx', the value will be set to 0.5*'xx' before performing GMT calculations. Only samples for which PBMC preparation was performed within 8 hours will be used for analysis.

"Below LOD" in IFN-γ and IL-4 data should be considered as "0".

"NR" in IFN-γ and IL-4 data should be considered as "not reportable" results.

Value of "< 100" and "IR" in Nab data due to hemolyzed samples should be considered as "not reportable" results.

">ULOQ" in Nab data are results above ULOQ at the maximal dilution and the ">ULOQ" value should be assigned as "64000".

7.1.3 Safety Assessments

7.1.3.1 Adverse Events

Immediate AEs are defined as any solicited local and systemic AEs and unsolicited AEs occurring within 30 minutes after vaccination. Multiple occurrences of the same event within a subject will be counted once in the maximum severity of symptoms category (potentially life threatening > severe > moderate > mild). Related is defined as AEs with a causality of "Definitely Related", "Probably Related" or "Possibly Related". Not related is defined as AEs with a causality of "Probably Not Related" or "Definitely Not Related".

Adverse events will be coded according to the MedDRA version 24.1.

(1) Duration of Adverse Events

Duration of Adverse Events (days) = AE stop date – AE start date + 1

7.1.3.1.1 Solicited Adverse Events

The PI assessment of a solicited adverse event will always be used when available.

In the event that both an e-diary and a paper diary were completed by the subject for the same solicited AE and the same timepoint, the record with the PI assessment will be used for analysis; otherwise, the paper diary data will be used in the analysis.

Scheduled day and timepoint, if applicable, will be used as record identifier(s) in solicited AE summaries.

7.1.3.1.1 Serious Adverse Events (SAE)

An SAE is any untoward medical occurrence (whether or not considered to be related to the study vaccine) that, at any dose:

- Results in death
- Is life-threatening (at the time of the event)
- Requires inpatient hospitalization (≥ 24 hours) or prolongation of existing hospitalization (elective hospitalizations/procedures for pre-existing conditions that have not worsened are excluded)
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect

7.1.3.1.2 Medically Attended Adverse Events (MAAE)

Medically attended adverse events are defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider.

7.1.3.1.3 Adverse Events of Special Interest (AESI)

7.1.3.1.3.1 Vaccine Associated Enhanced Disease (VAED)

Safety signal of VAED after exposure to the CoVLP formulation will be closely monitored and assessed by retrieving data for this AESI as follows: AEs within the system organ class (SOC): immune system disorders and high level group term (HLGT): lower respiratory tract disorders (excluding obstruction and infection), cardiac disorders, signs and symptoms not elsewhere classified, vascular disorders, heart failures, arteriosclerosis, stenosis, vascular insufficiency and necrosis, cardiac arrhythmias, myocardial disorders, and vascular hemorrhagic disorders. High level term (HLT): renal failure and impairment and preferred term (PT): pericarditis, coagulopathy, deep vein thrombosis, pulmonary embolism, cerebrovascular accidents, peripheral ischemia, liver injury, Guillain-Barre syndrome, anosmia, ageusia, encephalitis, chilblains, vasculitis, erythema multiforme that require inpatient hospitalization (≥ 24 hours) and have laboratory confirmed SARS-Cov-2 infection will be monitored for assessment of any

potential case of VAED. As this list can be updated during the study, any further changes to the AESI terms will be updated in the Signal Management Plan (SMP).

VAED list is attached in the Appendix.

7.1.3.1.3.2 Hypersensitivity Reactions (Anaphylaxis and Severe Allergic Reactions)

All reported events will also be monitored for related hypersensitivity reactions after exposure to the CoVLP formulation. Hypersensitivity will be identified using SMQ broad and narrow terms.

Hypersensitivity reaction list is attached in the Appendix.

7.1.3.1.3.3 Potential Immune-Mediated Diseases (pIMD)

Potential immune-mediated diseases (pIMDs) are a subset of AEs associated to the adjuvant that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. pIMDs will be identified using SMQ terms.

pIMD list is attached in the Appendix.

7.1.3.2 Laboratory Tests

(1) Laboratory values below the limit of quantification

1/2 LLOQ (lower limit of quantification) will be used for BLQ (below the limit of quantification) data in summary statistics.

7.2 Analysis Visit Definitions

The date of the first vaccination is defined as Day 0.

For the Day 21 visits, a window of +/-2 days will be applied to sample collection data. For the Day 24 visits, a time window is +/-1 days from the date of vaccination 2 + 3. For the Day 42 visits, a time window is +/-2 days from the date of vaccination 2 + 21. For the Day 128 visits, a time window is +/-14 days from the date of vaccination 2 + 107. For the Day 201 visits, a time window is +/-14 days from the date of vaccination 2 + 180. Subjects who have blood samples for immunogenicity taken outside of the time window for blood sample collection are to be excluded from the IPP set for the specific visit.

Unless otherwise specified, baseline will be the last observed value of the parameter of interest prior to the first vaccination. For post-baseline visit, if there are multiple data in a window, the later data will be used.

7.3 Data Handling Convention for Missing Data

Concomitant medication:

There is no imputation for completely missing dates.

Missing or partial concomitant medication start date:

- If only DAY is missing, use the first day of the month.
- If DAY and Month are both missing, use the first day of the year.

Missing or partial concomitant medication stop date:

- If only DAY is missing, use the last day of the month.
- If DAY and Month are both missing, use the last day of the year.
- If DAY, Month and year are all missing, assign 'continuing' status to stop date.

Immunogenicity:

Missing immunogenicity data will be retained as missing.

Adverse events:

There is no imputation for completely missing dates.
Missing or partial AE date:
No imputation of AE partial/missing start/end dates or times will be performed. In case of missing or incomplete AE onset date/time, the AE will be included in the analysis unless the incomplete AE onset date/time information unequivocally indicates that the AE started prior to Day 0.

If an AE allocation to a reporting cannot be unequivocally ascertained due to partial/missing date, the AE will be allocated to all relevant periods.
Missing relatedness and intensity of AEs will not be imputed and will be presented as "Missing".

Other safety:

For safety summaries, only observed data will be used. Unless otherwise specified, missing safety data will not be imputed.

8 STATISTICAL METHODOLOGY

8.1 Study Subjects

8.1.1 Subject Disposition and Analysis Population

Subject disposition will be presented for all the subjects.

Analysis populations will be summarized on the randomized population.

Randomization details will be listed on the randomized population. Subject disposition will be listed on the randomized population.

Analysis populations will be listed on the randomized population.

8.1.2 Demographic and Other Baseline Characteristics

The following demographic and other baseline characteristics will be used.

	category	descriptive
Gender	Male, Female	
Age(years)	< 65 >= 65	Yes
Height(cm)		Yes
Weight(kg)		Yes
BMI(kg/m^2)		Yes
Race	Japanese, Other	
Ethnicity	Hispanic or Latino, Not Hispanic or Latino	
Baseline SARS-CoV-2 antibody test	Positive, Negative	
Baseline SARS-CoV-2 PCR test	Positive, Negative	
Significant comorbidities	Yes, No	

Demographic and other baseline characteristics will be summarized on the Immunogenicity ITT set, Immunogenicity PP set and the SAS.

Other baseline characteristics will be listed on the randomized population.

8.1.3 Medical History

Medical history will be summarized on the SAS.

Medical history will be listed on the randomized population.

8.1.4 Prior or Concomitant Medications

Prior medication and concomitant medication (Up to Day 42 and after Day 43) will be summarized separately on the SAS.

Prior and concomitant medication will be listed on the SAS.

8.2 Immunogenicity Assessments

All immunogenicity data will be listed.

The following primary immunogenicity and safety endpoints are for Group 1 and Group 2.

8.2.1 Primary Immunogenicity Endpoint

8.2.1.1 Nab response against the SARS-CoV-2 virus

The following analyses for the Nab assay will be performed:

- GMT (Day 0, Day 21, and Day 42): The point estimates and the corresponding two-sided 95 % CI by treatment group will be calculated.
- SC rate (Day 21, and Day 42): The point estimates and the corresponding two-sided 95 % CI for subjects achieving SC by treatment group will be calculated.
- GMFR: the geometric mean of the ratio of GMTs (Day 21/Day 0 and Day 42/Day 0) will be calculated.

GMT will be compared between treatment groups using the analysis of variance (ANOVA) model.

<Sample SAS code>

[redacted]

For SC rate, Fisher's exact tests will be used to compare between the treatment groups, along with exact Clopper-Pearson 95% CI.

GMFR will be compared using the ANCOVA model. The GMFR will be derived by using ANCOVA to model the difference in the log of the titer values between Day 21 and Day 0 and

between Day 42 and Day 0, with treatment group as main effect and log-transformed baseline titer as covariate.

The reverse cumulative distribution (RCD) curve (plot % of population against the antibody titres) will be plotted and scatter plot will be created.

8.2.1.2 Specific Th1 CMI response against the SARS-CoV-2 virus measured by IFN-γ ELISpot

The specific Th1 CMI response on Day 0, Day 21, and Day 42 measured by IFN-γ ELISpot will be compared between treatment groups and timepoints. The Wilcoxon Rank Sum Test, also known as the Mann-Whitney Wilcoxon Test, will be used to estimate the difference in response between treatment groups, along with the corresponding 95% CI for the median and p-value.

Since the response between timepoints are paired data, the Wilcoxon Signed Rank Test will be used to estimate the difference in response between timepoints, along with the corresponding 95% CI for the median and p-value.

Scatter plot of the number of T cells expressing IFN-γ will be created.

8.2.1.3 Specific Th2 CMI response against the SARS-CoV-2 virus measured by IL-4 ELISpot

The specific Th2 CMI response on Day 0, Day 21, and Day 42 measured by IL-4 ELISpot will be compared between treatment groups and timepoints. The Wilcoxon Rank Sum Test will be used to estimate the difference in response between treatment groups, along with the corresponding 95% CI for the median and p-value.

The Wilcoxon Signed Rank Test will be used to estimate the difference in response between timepoints, along with the corresponding 95% CI for the median and p-value.

Scatter plot of the number of T cells expressing IL-4 will be created.

8.2.2 Secondary Immunogenicity Endpoints

8.2.2.1 Nab response against the SARS-CoV-2 virus

The following analyses for the Nab assay will be performed:

- GMT (Day 128 and Day 201): The point estimates and the corresponding two-sided 95 % CI by treatment group will be calculated.
- SC rate (Day 128 and Day 201): The point estimates and the corresponding two-sided 95 % CI for subjects achieving SC by treatment group will be calculated.
- GMFR: the geometric mean of the ratio of GMTs (Day 128/Day 0, Day 201/Day 0) will be calculated.

The same methodology as in section 8.2.1.1 will be used.

8.2.2.2 Specific Th1 CMI response against the SARS-CoV-2 virus measured by IFN-γ ELISpot

The specific Th1 CMI response induced on Day 201 will be analyzed according to the same methodology as in section 8.2.1.2.

8.2.2.3 Specific Th2 CMI response against the SARS-CoV-2 virus measured by IL-4 ELISpot

The specific Th2 CMI response induced on Day 201 will be analyzed according to the same methodology as in section 8.2.1.3.

8.2.2.4 Specific antibody response against the SARS-CoV-2 virus by the total IgG levels

The GMT will be calculated on Day 0, Day 21, Day 42 and Day 201 as well as the GMFR (Day 21/Day 0, Day 42/Day 0, Day 201/Day 0). SC rate will be calculated on Day 21, Day 42 and Day 201.

GMT will be compared between treatment groups using the analysis of variance (ANOVA) model.

For SC rate, Fisher's exact test will be used to compare between the treatment groups, along with exact Clopper-Pearson 95% CI.

GMFR will be compared using the ANCOVA model. The GMFR will be derived by using ANCOVA to model the difference in the log of the titer values between Day 21 and Day 0, between Day 42 and Day 0, between Day 201 and Day 0 with treatment group as main effect and log-transformed baseline titer as covariate.

The RCD curve will be plotted.

8.2.3 Specific CMI response against the SARS-CoV-2 virus measured by the percentage of CD4+ T cells expressing functional markers

The CMI response on Day 0, Day 21 and Day 42 measured by the percentage of T cells expressing functional markers, using flow cytometry will be compared between treatment groups and timepoints. The Wilcoxon Rank Sum Test will be used to estimate the difference in response between treatment groups, along with the corresponding 95% CI for the median.

The Wilcoxon Signed Rank Test will be used to estimate the difference in response between timepoints, along with the corresponding 95% CI for the median.

Parameters
CD4+CD8- > IL2+ percent of CD4, CD4+CD8- > IL4+ percent of CD4, CD154+ > IFN_TNF_IL2_Poly percent of CD4, CD4+CD8- > IFN_TNF_IL2_Poly percent of CD4

8.2.3.1 Specific antibody response against plant glycans measured by serum IgE levels

The specific antibody response against plant glycans induced on Day 0, Day 42 and Day 201 will be analyzed by evaluating the percentage of subjects with detectable IgE levels at each timepoint for each treatment group and the percentage of subjects with undetectable IgE levels at each timepoint for each treatment group along with corresponding two-sided 95% exact (Clopper-Pearson method). The difference in percentage between Day 42 and Day 0, Day 201 and Day 0 and associated 95% CI for the difference will be calculated for each treatment group.

8.2.4 Other Immunogenicity Endpoints

8.2.4.1 The ratio of neutralizing antibody titers: IgG ELISA antibody titers

The Nab/IgG ratio will be calculated as the antilog of the Nab/IgG ratio and 95 % CI of log transformed titer values. The ratio will be compared between treatment groups using ANOVA.

8.3 Safety Assessments

All safety data will be listed.

Safety assessments will be made on the SAS.

Adverse events analyses will be presented for the following reporting period, as applicable:

- Day 0-21 period after vaccination 1: Any AEs meeting the following criteria will be allocated to the first vaccination (vaccination 1) and included in the Day 0-21 analysis for first vaccination:
  - Any AEs with:
    - onset date/time < date and time of second vaccine administration, if second vaccination is done,
    - else if vaccination 2 not performed, any AEs with onset date ≤ date of vaccination 1+ 21
- Day 0-21 period after vaccination 2: Any AEs meeting the following criteria will be allocated to second vaccination (vaccination 2) and included in the Day 0-21 analysis for second vaccination:
  - Any AEs with onset date/time ≥ Date/time of vaccination 2 and with onset date ≤ date of vaccination 2 + 21.

- Day 0-21 period after last vaccination: Any AEs meeting the following criteria will be included in the Day 0-21 period after last vaccination:
  - Any AEs with onset date ≤ date of last vaccination + 21 i.e.:
    - Any AEs with onset date ≤ date of vaccination 2 + 21, if vaccination 2 is performed
  - Any AEs with onset date ≤ date of vaccination 1 + 21, if vaccination 2 is not performed.

8.3.1 Primary Safety Endpoint

8.3.1.1 The incidences and severity of the solicited AEs

The incidences and severity of solicited AEs will be summarized by treatment using descriptive statistics.

8.3.1.2 The incidences, severity, and investigator-assessed causality of unsolicited AEs

The incidences, severity and relationship of unsolicited AEs will be summarized by treatment using descriptive statistics.

8.3.1.3 The incidences of serious AEs (SAEs), medically attended AEs (MAAEs), AEs leading to withdrawal, AEs of special interest (AESIs), and deaths

The incidences of serious AEs (SAEs), medically attended AEs (MAAEs), AEs leading to withdrawal, AEs of special interest (AESIs), and deaths will be summarized by treatment using descriptive statistics.

8.3.2 Adverse Events

Overall summary will be conducted through primary safety endpoint.

Overall summary of safety for each Day 0-21 vaccination period:

- Any Immediate AEs (occurring within 30 minutes after vaccination):
  - Immediate solicited AE;
    - Solicited injection site AE
    - Solicited systemic AE
  - Immediate unsolicited AE;
- Any solicited AE:
  - ≥ Grade 3 Solicited AEs;
  - Solicited Local AEs
  - Solicited systemic AE;
- Unsolicited AEs;
  - ≥ Grade 3 unsolicited AEs;
- Serious AEs;
- Related Serious AEs

- Medically Attended AEs;
- Related Medically Attended AEs;
- AEs leading to study withdrawal
- AESI: Overall, VED, Hypersensitivity, potential immune-mediated diseases
- AEs leading to death

Overall summary of safety for up to EOS:

- Unsolicited AEs;
  - ≥ Grade 3 unsolicited AEs;
- Serious AEs;
- Related Serious AEs
- Medically Attended AEs;
- Related Medically Attended AEs;
- AEs leading to study withdrawal
- AESI: Overall, VED, Hypersensitivity, potential immune-mediated diseases
- AEs leading to death

8.3.2.1 Solicited Local and Systemic Adverse Events

Solicited local and systemic AEs will be summarized through primary safety endpoint for each of the following for overall.

- Solicited local and systemic AEs within first seven days after each vaccination

8.3.2.2 Unsolicited Adverse Events

All spontaneous unsolicited AEs will be classified by system organ class (SOC) and preferred term (PT) for each of the following by overall. Unsolicited AEs will be summarized through primary safety endpoint. Most frequent AEs are defined as those that occur > 5% of either of the treatment groups and will only be summarized by PT.

- Most frequent unsolicited AEs
- AESIs
- SAEs
- MAAEs
- AEs leading to death
- AEs leading to withdrawal

8.3.3 Laboratory Tests

Laboratory Test	Parameters
Hematology	Haemoglobin, Hematocrit, Red blood cell, Platelets, Mean platelet volume (MPV), White cell count (total, WBC), Neutrophils, Mean cell haemoglobin (MCH), Mean cell concentration (MCHC), Mean cell volume (MCV), Lymphocytes, Monocytes, Eosinophils, Basophils
Biochemistry	Sodium, Potassium, Urea, Creatinine, Glucose, Bilirubin (total), Albumin, Total protein, Alkaline phosphatase, Alaninetransferase (ALT), Aspartatetransferase (AST), Gamma glutamyltransferase (GGT), Cholesterol (total, HDL, LDL), Triglyceride, Chloride, Calcium, Phosphorus
Urinalysis	Macroscopic examination (color, aspect), pH, Specific gravity, Glucose, Protein, Blood
Other	SARS-CoV-2 IgG Antibody, Hepatitis B Virus Surface Antigen, Hepatitis C Virus Antibody

8.3.4 Vital Signs

Absolute values and changes from baseline will be summarized for the following parameters.

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (beats/min)
- Respiratory Rate (breaths/min)
- Oral Temperature(°C)

8.3.5 Physical Examinations

Physical examination will be summarized.

9 DATA PRESENTATION CONVENTIONS

9.1 Number of Digits to Report

Statistic	Specification	Apply to
Minimum, Maximum	Same number of DPs as the data provided in the datasets	All original (i.e. non-derived)
	see section 7.3	All derived data
Mean, Median, SD, SE, Confidence intervals	One more DP than above	All
Percentages[1]	1 DP	All
Ratios	3 DPs	All
p-values[2]	3 DPs	All

[1] Percentages: use 1 place beyond the decimal point, except for the following cases:
If the percentage is equal to 0, then leave blank, do not use (0)
If the percentage is equal to 100, then use "(100)" without a decimal

[2] p-values: use 3 places beyond the decimal point, except for the following cases:
If the p-value is less than 0.001, then use p<0.001

9.2 Treatment Groups to Report

Treatment Group	For TFLs
3.75 µg MT-2766	MT-2766 3.75 µg
Placebo	Placebo

9.3 Analysis Visits to Report

Immunogenicity:

Analysis Visit	Apply to
Day 0	All immunogenicity
Day 21	All immunogenicity
Day 42	All immunogenicity
Day 128	All immunogenicity (except for CMI response)
Day 201	All immunogenicity (except for CMI response measured by the percentage of T cells)

Safety:

Analysis Visit	**Apply to**
Day 0	All Laboratory Tests
Day 3	All Laboratory Tests
Day 21	All Laboratory Tests
Day 24	All Laboratory Tests
Day 42	All Laboratory Tests

Analysis Visit	**Analysis Time Point**	**Apply to**	
		Vital Signs	Physical Examination
Day 0	Before vaccination	X	X
	After vaccination	X	X
Day 3		X	X
Day 21	Before vaccination	X	X
	After vaccination	X	X
Day 24		X	X
Day 42		X	X
Day 128		X	X
Day 201		X	X

Unscheduled visits, retests (same visit number assigned) and follow-up visits will not be displayed in by-visit summary tables, but will be included in the data listings.

10 CHANGE FROM THE PROTOCOL

Group 3 was not enrolled. Also, because the study was discontinued, the items on Day 386 and some items were not measured. Only the collected data were included in the tabulation and listings.

11 SOFTWARE

All statistical analyses will be performed using SAS version 9.4 or higher.

12 REFERENCES

N/A

APPENDIX 1 SEVERITY GRADES FOR SOLICITED LOCAL AND SYSTEMIC ADVERSE EVENTS

Symptoms	Severity				
	None	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially life-threatening)
Injection Site Adverse Events (Local Adverse Events)					
Erythema (redness)	< 25 mm	25 - 50 mm	51 - 100 mm	> 100 mm	Necrosis or exfoliative dermatitis
Swelling	< 25 mm	25 - 50 mm and does not interfere with activity	51 – 100 mm or interferes with activity	> 100 mm or prevents daily activity	Necrosis
Pain	None	Does not interfere with activity	Repeated use of non-narcotic pain reliever for more than 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Solicited Systemic Adverse Events					
Fever (°C or °F)	< 38.0 °C < 100.4 °F	38.0 - 38.4 °C 100.4 - 101.1 °F	38.5 - 38.9 °C 101.2 - 102.0 °F	39.0 - 40.0 °C 102.1 - 104.0 °F	> 40.0 °C > 104.0 °F
Headache	None	No interference with activity	Repeated use of non-narcotic pain reliever for more than 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Muscle aches	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Joint aches, chills, feeling of general discomfort or uneasiness (malaise), swelling in the axilla, swelling in the neck	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Results in a visit to emergency room (ER) or hospitalization

APPENDIX 2 VAED

PT	PT Code
Asymptomatic COVID-19	10084459
Congenital COVID-19	10085080
Coronavirus infection	10051905
Coronavirus pneumonia	10084381
Coronavirus test positive	10070255
COVID-19	10084268
COVID-19 immunisation	10084457
COVID-19 pneumonia	10084380
COVID-19 prophylaxis	10084458
COVID-19 treatment	10084460
Exposure to SARS-CoV-2	10084456
Multisystem inflammatory syndrome	10086091
Multisystem inflammatory syndrome in adults	10085850
Multisystem inflammatory syndrome in children	10084767
Occupational exposure to SARS-CoV-2	10084394
Post-acute COVID-19 syndrome	10085503
SARS-CoV-2 antibody test positive	10084491
SARS-CoV-2 carrier	10084461
SARS-CoV-2 RNA decreased	10085496
SARS-CoV-2 RNA fluctuation	10085497
SARS-CoV-2 RNA increased	10085495
SARS-CoV-2 sepsis	10084639
SARS-CoV-2 test false negative	10084480
SARS-CoV-2 test positive	10084271
SARS-CoV-2 viraemia	10084640
Suspected COVID-19	10084451
Thrombosis with thrombocytopenia syndrome	10086158
Vaccine derived SARS-CoV-2 infection	10085492

APPENDIX 3 HYPERSENSITIVITY REACTIONS

PT	PT Code
Acquired C1 inhibitor deficiency	10081035
Acute generalised exanthematous pustulosis	10048799
Administration related reaction	10069773
Administration site dermatitis	10075096
Administration site eczema	10075099
Administration site hypersensitivity	10075102
Administration site rash	10071156
Administration site recall reaction	10075964
Administration site urticaria	10075109
Administration site vasculitis	10075969
Allergic bronchitis	10052613
Allergic colitis	10059447
Allergic cough	10053779
Allergic cystitis	10051394
Allergic eosinophilia	10075185
Allergic gastroenteritis	10075308
Allergic hepatitis	10071198
Allergic keratitis	10057380
Allergic lymphangitis	10086007
Allergic oedema	10060934
Allergic otitis externa	10075072
Allergic otitis media	10061557
Allergic pharyngitis	10050639
Allergic reaction to excipient	10078853
Allergic respiratory disease	10063532
Allergic respiratory symptom	10063527
Allergic sinusitis	10049153
Allergic stomatitis	10079554
Allergic transfusion reaction	10066173
Allergy alert test positive	10075479
Allergy test positive	10056352
Allergy to immunoglobulin therapy	10074079
Allergy to surgical sutures	10077279
Allergy to vaccine	10055048
Anal eczema	10078682
Anaphylactic reaction	10002198
Anaphylactic shock	10002199
Anaphylactic transfusion reaction	10067113

Anaphylactoid reaction	10002216
Anaphylactoid shock	10063119
Anaphylaxis treatment	10002222
Angioedema	10002424
Antiallergic therapy	10064059
Antiendomysial antibody positive	10065514
Anti-neutrophil cytoplasmic antibody positive vasculitis	10050894
Application site dermatitis	10003036
Application site eczema	10050099
Application site hypersensitivity	10063683
Application site rash	10003054
Application site recall reaction	10076024
Application site urticaria	10050104
Application site vasculitis	10076027
Arthritis allergic	10061430
Aspirin-exacerbated respiratory disease	10075084
Atopic cough	10081492
Atopy	10003645
Blepharitis allergic	10005149
Blood immunoglobulin E abnormal	10005589
Blood immunoglobulin E increased	10005591
Bromoderma	10006404
Bronchospasm	10006482
Bullous haemorrhagic dermatosis	10083809
Catheter site dermatitis	10073992
Catheter site eczema	10073995
Catheter site hypersensitivity	10073998
Catheter site rash	10052271
Catheter site urticaria	10052272
Catheter site vasculitis	10074014
Chronic eosinophilic rhinosinusitis	10071399
Chronic hyperplastic eosinophilic sinusitis	10071380
Circulatory collapse	10009192
Circumoral oedema	10052250
Circumoral swelling	10081703
Conjunctival oedema	10010726
Conjunctivitis allergic	10010744
Contact stomatitis	10067510
Contrast media allergy	10066973
Contrast media reaction	10010836

Corneal oedema	10011033
Cross sensitivity reaction	10011411
Cutaneous vasculitis	10011686
Dennie-Morgan fold	10062918
Dermatitis	10012431
Dermatitis acneiform	10012432
Dermatitis allergic	10012434
Dermatitis atopic	10012438
Dermatitis bullous	10012441
Dermatitis contact	10012442
Dermatitis exfoliative	10012455
Dermatitis exfoliative generalised	10012456
Dermatitis herpetiformis	10012468
Dermatitis infected	10012470
Dermatitis psoriasiform	10058675
Device allergy	10072867
Dialysis membrane reaction	10076665
Distributive shock	10070559
Documented hypersensitivity to administered product	10076470
Drug eruption	10013687
Drug hypersensitivity	10013700
Drug provocation test	10074350
Drug reaction with eosinophilia and systemic symptoms	10073508
Eczema	10014184
Eczema infantile	10014198
Eczema nummular	10014201
Eczema vaccinatum	10066042
Eczema vesicular	10058681
Eczema weeping	10055182
Encephalitis allergic	10056387
Encephalopathy allergic	10014627
Eosinophilic granulomatosis with polyangiitis	10078117
Epidermal necrosis	10059284
Epidermolysis	10053177
Epidermolysis bullosa	10014989
Epiglottic oedema	10015029
Erythema multiforme	10015218
Erythema nodosum	10015226
Exfoliative rash	10064579

Eye allergy	10015907
Eye oedema	10052139
Eye swelling	10015967
Eyelid oedema	10015993
Face oedema	10016029
Fixed eruption	10016741
Generalised bullous fixed drug eruption	10084905
Giant papillary conjunctivitis	10018258
Gingival oedema	10049305
Gingival swelling	10018291
Gleich's syndrome	10066837
Haemorrhagic urticaria	10059499
Hand dermatitis	10058898
Henoch-Schonlein purpura	10019617
Henoch-Schonlein purpura nephritis	10069440
Heparin-induced thrombocytopenia	10062506
Hypersensitivity	10020751
Hypersensitivity myocarditis	10081004
Hypersensitivity pneumonitis	10081988
Hypersensitivity vasculitis	10020764
Idiopathic urticaria	10021247
Immediate post-injection reaction	10067142
Immune thrombocytopenia	10083842
Immune tolerance induction	10070581
Implant site dermatitis	10063855
Implant site hypersensitivity	10063858
Implant site rash	10063786
Implant site urticaria	10063787
Incision site dermatitis	10073168
Incision site rash	10073411
Infusion related hypersensitivity reaction	10082742
Infusion related reaction	10051792
Infusion site dermatitis	10065458
Infusion site eczema	10074850
Infusion site hypersensitivity	10065471
Infusion site rash	10059830
Infusion site recall reaction	10076085
Infusion site urticaria	10065490
Infusion site vasculitis	10074851
Injection related reaction	10071152
Injection site dermatitis	10022056

Injection site eczema	10066221
Injection site hypersensitivity	10022071
Injection site rash	10022094
Injection site recall reaction	10066797
Injection site urticaria	10022107
Injection site vasculitis	10067995
Instillation site hypersensitivity	10073612
Instillation site rash	10073622
Instillation site urticaria	10073627
Interstitial granulomatous dermatitis	10067972
Intestinal angioedema	10076229
Iodine allergy	10052098
Kounis syndrome	10069167
Laryngeal oedema	10023845
Laryngitis allergic	10064866
Laryngospasm	10023891
Laryngotracheal oedema	10023893
Limbal swelling	10070492
Lip oedema	10024558
Lip swelling	10024570
Mast cell activation syndrome	10075217
Mast cell degranulation present	10076606
Medical device site dermatitis	10075572
Medical device site eczema	10075575
Medical device site hypersensitivity	10075579
Medical device site rash	10075585
Medical device site recall reaction	10076140
Medical device site urticaria	10075588
Mouth swelling	10075203
Mucocutaneous rash	10056671
Multiple allergies	10028164
Nephritis allergic	10029120
Nikolsky's sign	10029415
Nodular rash	10075807
Nutritional supplement allergy	10084049
Oculomucocutaneous syndrome	10030081
Oculorespiratory syndrome	10067317
Oedema mouth	10030110
Oral allergy syndrome	10068355
Oropharyngeal blistering	10067950
Oropharyngeal oedema	10078783

Oropharyngeal spasm	10031111
Oropharyngeal swelling	10031118
Palatal oedema	10056998
Palatal swelling	10074403
Palisaded neutrophilic granulomatous dermatitis	10068809
Palpable purpura	10056872
Pathergy reaction	10074332
Perioral dermatitis	10034541
Periorbital oedema	10034545
Periorbital swelling	10056647
Pharyngeal oedema	10034829
Pharyngeal swelling	10082270
Polymers allergy	10086347
Procedural shock	10080894
Pruritus allergic	10063438
Radioallergosorbent test positive	10037789
Rash	10037844
Rash erythematous	10037855
Rash follicular	10037857
Rash macular	10037867
Rash maculo-papular	10037868
Rash maculovesicular	10050004
Rash morbilliform	10037870
Rash neonatal	10037871
Rash papulosquamous	10037879
Rash pruritic	10037884
Rash pustular	10037888
Rash rubelliform	10057984
Rash scarlatiniform	10037890
Rash vesicular	10037898
Reaction to azo-dyes	10037973
Reaction to colouring	10037974
Reaction to excipient	10079925
Reaction to food additive	10037977
Reaction to preservatives	10064788
Red man syndrome	10038192
Rhinitis allergic	10039085
Scleral oedema	10057431
Scleritis allergic	10051126
Scrotal dermatitis	10083260
Scrotal oedema	10039755

Serum sickness	10040400
Serum sickness-like reaction	10040402
Shock	10040560
Shock symptom	10040581
SJS-TEN overlap	10083164
Skin necrosis	10040893
Skin reaction	10040914
Skin test positive	10040934
Solar urticaria	10041307
Solvent sensitivity	10041316
Stevens-Johnson syndrome	10042033
Stoma site hypersensitivity	10074509
Stoma site rash	10059071
Swelling face	10042682
Swelling of eyelid	10042690
Swollen tongue	10042727
Symmetrical drug-related intertriginous and flexural exanthema	10078325
Tongue oedema	10043967
Toxic epidermal necrolysis	10044223
Toxic skin eruption	10057970
Tracheal oedema	10044296
Type I hypersensitivity	10045240
Type II hypersensitivity	10054000
Type III immune complex mediated reaction	10053614
Type IV hypersensitivity reaction	10053613
Urticaria	10046735
Urticaria cholinergic	10046740
Urticaria chronic	10052568
Urticaria contact	10046742
Urticaria papular	10046750
Urticaria physical	10046751
Urticaria pigmentosa	10046752
Urticaria vesiculosa	10046755
Urticarial dermatitis	10082290
Urticarial vasculitis	10048820
Vaccination site dermatitis	10069477
Vaccination site eczema	10076161
Vaccination site exfoliation	10069489
Vaccination site hypersensitivity	10068880
Vaccination site rash	10069482

Vaccination site recall reaction	10076188
Vaccination site urticaria	10069622
Vaccination site vasculitis	10076191
Vaccination site vesicles	10069623
Vaginal ulceration	10046943
Vascular access site dermatitis	10085938
Vascular access site eczema	10085939
Vasculitic rash	10047111
Vernal keratoconjunctivitis	10081000
Vessel puncture site rash	10077117
Vessel puncture site vesicles	10077813
Vulval eczema	10066273
Vulval ulceration	10047768
Vulvovaginal rash	10071588
Vulvovaginal ulceration	10050181
Vulvovaginitis allergic	10080783
Acute respiratory failure	10001053
Administration site photosensitivity reaction	10075961
Airway remodelling	10075289
Allergy to chemicals	10061626
Allergy to fermented products	10054929
Alpha tumour necrosis factor increased	10059982
Alveolitis	10001889
Antibody test abnormal	10061425
Antibody test positive	10061427
Anti-insulin antibody increased	10053815
Anti-insulin antibody positive	10053814
Anti-insulin receptor antibody increased	10068226
Anti-insulin receptor antibody positive	10068225
Application site photosensitivity reaction	10058730
Asthma	10003553
Asthma late onset	10003559
Asthma-chronic obstructive pulmonary disease overlap syndrome	10077005
Asthmatic crisis	10064823
Auricular swelling	10003800
Blister	10005191
Blister rupture	10073385
Blood immunoglobulin A abnormal	10005584
Blood immunoglobulin A increased	10005586
Blood immunoglobulin D increased	10063244

Blood immunoglobulin G abnormal	10005594
Blood immunoglobulin G increased	10005596
Blood immunoglobulin M abnormal	10005599
Blood immunoglobulin M increased	10005601
Bronchial hyperreactivity	10066091
Bronchial oedema	10056695
Bullous impetigo	10006563
Caffeine allergy	10074895
Capillaritis	10068406
Charcot-Leyden crystals	10008413
Cheilitis	10008417
Childhood asthma	10081274
Choking	10008589
Choking sensation	10008590
Complement factor C1 decreased	10051552
Complement factor C2 decreased	10051555
Complement factor C3 decreased	10050981
Complement factor C4 decreased	10050983
Complement factor decreased	10061048
Conjunctivitis	10010741
Corneal exfoliation	10064489
Cough variant asthma	10063076
Cytokine increased	10085573
Cytokine release syndrome	10052015
Cytokine storm	10050685
Ear swelling	10014025
Eosinophil count abnormal	10061125
Eosinophil count increased	10014945
Eosinophil percentage abnormal	10058133
Eosinophil percentage increased	10052222
Eosinophilia	10014950
Eosinophilia myalgia syndrome	10014952
Eosinophilic bronchitis	10065563
Eosinophilic oesophagitis	10064212
Eosinophilic pneumonia	10014962
Eosinophilic pneumonia acute	10052832
Eosinophilic pneumonia chronic	10052833
Erythema	10015150
Flushing	10016825
Foreskin oedema	10085613
Gastrointestinal oedema	10058061

Generalised oedema	10018092
Genital rash	10018175
Genital swelling	10067639
Haemolytic transfusion reaction	10067122
HLA marker study positive	10067937
Human anti-hamster antibody increased	10082107
Human anti-hamster antibody positive	10082109
Immune complex level increased	10064650
Immunoglobulins abnormal	10021497
Immunoglobulins increased	10021500
Immunology test abnormal	10061214
Implant site photosensitivity	10073415
Infusion site photosensitivity reaction	10065486
Injection site panniculitis	10083040
Injection site photosensitivity reaction	10053396
Interstitial lung disease	10022611
Laryngeal dyspnoea	10052390
Laryngeal obstruction	10059639
Leukotriene increased	10064663
Lip exfoliation	10064482
Localised oedema	10048961
Macrophage inflammatory protein-1 alpha increased	10083049
Mechanical urticaria	10068773
Medical device site photosensitivity reaction	10076137
Mesenteric panniculitis	10063031
Monocyte chemotactic protein-2 increased	10083043
Mouth ulceration	10028034
Mucocutaneous ulceration	10028084
Mucosa vesicle	10028103
Mucosal erosion	10061297
Mucosal exfoliation	10064486
Mucosal necrosis	10067993
Mucosal ulceration	10028124
Nasal crease	10078581
Necrotising panniculitis	10062579
Neurodermatitis	10029263
Neutralising antibodies positive	10064980
Noninfective conjunctivitis	10074701
Non-neutralising antibodies positive	10064982
Occupational asthma	10070836

Occupational dermatitis	10030012
Oedema mucosal	10030111
Oral mucosal exfoliation	10064487
Orbital oedema	10031051
Panniculitis	10033675
Penile exfoliation	10064485
Penile oedema	10066774
Penile rash	10082571
Penile swelling	10034319
Perineal rash	10075364
Perivascular dermatitis	10064986
Photosensitivity reaction	10034972
Pneumonitis	10035742
Prurigo	10037083
Pruritus	10037087
Pulmonary eosinophilia	10037382
Reactive airways dysfunction syndrome	10070832
Respiratory arrest	10038669
Respiratory distress	10038687
Respiratory failure	10038695
Respiratory tract oedema	10070774
Reversible airways obstruction	10062109
Rhinitis perennial	10039094
Scrotal exfoliation	10081178
Scrotal swelling	10039759
Seasonal allergy	10048908
Septal panniculitis	10056876
Skin erosion	10040840
Skin exfoliation	10040844
Skin oedema	10058679
Skin swelling	10053262
Sneezing	10041232
Status asthmaticus	10041961
Stomatitis	10042128
Streptokinase antibody increased	10053797
Stridor	10042241
Suffocation feeling	10042444
Sunscreen sensitivity	10083629
Throat tightness	10043528
Tongue exfoliation	10064488
Tracheal obstruction	10044291

Tracheostomy	10044320
Transplantation associated food allergy	10075008
Upper airway obstruction	10067775
Vaccination site photosensitivity reaction	10076186
Vaccine associated enhanced disease	10085491
Vaccine associated enhanced respiratory disease	10085001
Vaginal oedema	10063818
Visceral oedema	10065768
Vulval oedema	10047763
Vulvovaginal exfoliation	10083435
Vulvovaginal swelling	10071211
Wheezing	10047924

APPENDIX 4 PIMD

PT
Acute cutaneous lupus erythematosus
Acute disseminated encephalomyelitis
Acute febrile neutrophilic dermatosis
Acute flaccid myelitis
Acute haemorrhagic leukoencephalitis
Acute haemorrhagic oedema of infancy
Acute macular neuroretinopathy
Acute motor axonal neuropathy
Acute motor-sensory axonal neuropathy
Acute necrotising myelitis
Addison's disease
Administration site vasculitis
Alopecia areata
Alveolar proteinosis
Ankylosing spondylitis
Anti-glomerular basement membrane disease
Anti-LRP2 nephropathy
Anti-myelin-associated glycoprotein associated polyneuropathy
Anti-neutrophil cytoplasmic antibody positive vasculitis
Antiphospholipid syndrome
Anti-RNA polymerase III antibody increased
Anti-RNA polymerase III antibody positive
Antisynthetase syndrome
Aortitis
Application site vasculitis
Arteritis
Arteritis coronary
Arthritis enteropathic
Arthritis reactive
Atrophic thyroiditis
Autoimmune anaemia
Autoimmune aplastic anaemia
Autoimmune arthritis
Autoimmune blistering disease
Autoimmune cholangitis
Autoimmune colitis
Autoimmune demyelinating disease

Autoimmune dermatitis
Autoimmune disorder
Autoimmune encephalopathy
Autoimmune endocrine disorder
Autoimmune enteropathy
Autoimmune eye disorder
Autoimmune haemolytic anaemia
Autoimmune heparin-induced thrombocytopenia
Autoimmune hepatitis
Autoimmune hyperlipidaemia
Autoimmune hypothyroidism
Autoimmune inner ear disease
Autoimmune lung disease
Autoimmune lymphoproliferative syndrome
Autoimmune myocarditis
Autoimmune myositis
Autoimmune nephritis
Autoimmune neuropathy
Autoimmune neutropenia
Autoimmune pancreatitis
Autoimmune pancytopenia
Autoimmune pericarditis
Autoimmune retinopathy
Autoimmune thyroid disorder
Autoimmune thyroiditis
Autoimmune uveitis
Autoinflammatory disease
Axial spondyloarthritis
Axonal and demyelinating polyneuropathy
Axonal neuropathy
Basedow's disease
Behcet's syndrome
Bell's palsy
Bickerstaff's encephalitis
Birdshot chorioretinopathy
Brachial plexopathy
Bulbar palsy
C1q nephropathy
Capillaritis
Capillary leak syndrome
Caplan's syndrome

Cardiac sarcoidosis
Central nervous system lupus
Central nervous system vasculitis
Cerebral arteritis
Cholangitis sclerosing
Chronic autoimmune glomerulonephritis
Chronic cutaneous lupus erythematosus
Chronic inflammatory demyelinating polyradiculoneuropathy
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids
Chronic pigmented purpura
Clinically isolated syndrome
Coeliac disease
Cogan's syndrome
Cold type haemolytic anaemia
Colitis erosive
Colitis microscopic
Colitis ulcerative
Collagen-vascular disease
Concentric sclerosis
Coombs positive haemolytic anaemia
Cranial nerve disorder
Cranial nerve palsies multiple
Cranial nerve paralysis
CREST syndrome
Crohn's disease
Cutaneous lupus erythematosus
Cutaneous sarcoidosis
Cutaneous vasculitis
Demyelinating polyneuropathy
Demyelination
Dermatitis bullous
Dermatitis herpetiformis
Dermatomyositis
Diffuse vasculitis
Encephalitis allergic
Encephalitis autoimmune
Encephalitis brain stem
Encephalitis haemorrhagic
Encephalitis periaxialis diffusa

Encephalitis post immunisation
Encephalitis toxic
Encephalomyelitis
Endocrine ophthalmopathy
Enteropathic spondylitis
Eosinophilic fasciitis
Eosinophilic granulomatosis with polyangiitis
Erythema induratum
Erythema multiforme
Erythema nodosum
Evans syndrome
Expanded disability status scale score decreased
Expanded disability status scale score increased
Facial paralysis
Facial paresis
Felty's syndrome
Fibrillary glomerulonephritis
Fulminant type 1 diabetes mellitus
Giant cell arteritis
Giant cell myocarditis
Glomerulonephritis membranoproliferative
Glomerulonephritis membranous
Glomerulonephritis rapidly progressive
Glossopharyngeal nerve paralysis
Goodpasture's syndrome
Gout
Gouty arthritis
Gouty tophus
Granulomatosis with polyangiitis
Granulomatous dermatitis
Guillain-Barre syndrome
Haemorrhagic occlusive retinal vasculitis
Haemorrhagic vasculitis
Hashimoto's encephalopathy
Hashitoxicosis
Henoch-Schonlein purpura
Henoch-Schonlein purpura nephritis
Hypersensitivity vasculitis
Hypoglossal nerve paralysis
Hypoglossal nerve paresis
Idiopathic inflammatory myopathy

Idiopathic interstitial pneumonia
Idiopathic pulmonary fibrosis
IgA nephropathy
IgM nephropathy
IIIrd nerve paralysis
IIIrd nerve paresis
Immune thrombocytopenia
Immune-mediated adrenal insufficiency
Immune-mediated adverse reaction
Immune-mediated arthritis
Immune-mediated cholangitis
Immune-mediated cholestasis
Immune-mediated cystitis
Immune-mediated cytopenia
Immune-mediated dermatitis
Immune-mediated encephalitis
Immune-mediated encephalopathy
Immune-mediated endocrinopathy
Immune-mediated enterocolitis
Immune-mediated gastritis
Immune-mediated hepatic disorder
Immune-mediated hepatitis
Immune-mediated hyperthyroidism
Immune-mediated hypophysitis
Immune-mediated hypothyroidism
Immune-mediated lung disease
Immune-mediated myocarditis
Immune-mediated myositis
Immune-mediated nephritis
Immune-mediated neurological disorder
Immune-mediated neuropathy
Immune-mediated oesophagitis
Immune-mediated pancreatitis
Immune-mediated renal disorder
Immune-mediated thyroiditis
Immune-mediated uveitis
Immunoglobulin G4 related disease
Inclusion body myositis
Inflammatory bowel disease
Injection site vasculitis
Insulin autoimmune syndrome

Interstitial granulomatous dermatitis
Interstitial lung disease
Intramyelinic oedema
IVth nerve paralysis
IVth nerve paresis
Juvenile idiopathic arthritis
Juvenile polymyositis
Juvenile psoriatic arthritis
Juvenile spondyloarthritis
Kawasaki's disease
Keratoderma blenorrhagica
Langerhans' cell histiocytosis
Laryngeal rheumatoid arthritis
Latent autoimmune diabetes in adults
Leukoencephalomyelitis
Leukoencephalopathy
Lewis-Sumner syndrome
Lichen planopilaris
Lichen planus
Limbic encephalitis
Linear IgA disease
Liver sarcoidosis
Loefgren syndrome
Lumbosacral radiculoplexus neuropathy
Lupoid hepatic cirrhosis
Lupus anticoagulant hypoprothrombinaemia syndrome
Lupus cystitis
Lupus encephalitis
Lupus endocarditis
Lupus enteritis
Lupus hepatitis
Lupus myocarditis
Lupus myositis
Lupus nephritis
Lupus pancreatitis
Lupus pleurisy
Lupus pneumonitis
Lupus vasculitis
Lupus-like syndrome
Lymphocytic hypophysitis

MAGIC syndrome
Marburg's variant multiple sclerosis
Marine Lenhart syndrome
Melkersson-Rosenthal syndrome
Membranous-like glomerulopathy with masked IgG-kappa deposits
Mesangioproliferative glomerulonephritis
Metastatic cutaneous Crohn's disease
Microscopic enteritis
Microscopic polyangiitis
Miller Fisher syndrome
Mixed connective tissue disease
Mononeuritis
Mononeuropathy multiplex
Morphoea
Multifocal motor neuropathy
Multiple sclerosis
Multiple sclerosis pseudo relapse
Multiple sclerosis relapse
Multiple sclerosis relapse prophylaxis
Multisystem inflammatory syndrome
Multisystem inflammatory syndrome in adults
Multisystem inflammatory syndrome in children
Muscular sarcoidosis
Myasthenia gravis
Myasthenia gravis crisis
Myasthenic syndrome
Myelin oligodendrocyte glycoprotein antibody-associated disease
Myelitis
Myelitis transverse
Myocarditis
Narcolepsy
Neuralgic amyotrophy
Neuritis
Neuritis cranial
Neuromyelitis optica pseudo relapse
Neuromyelitis optica spectrum disorder
Neuropsychiatric lupus
Neurosarcoidosis
Nodular vasculitis

Noninfectious myelitis
Noninfective encephalitis
Noninfective encephalomyelitis
Ocular myasthenia
Ocular pemphigoid
Ocular sarcoidosis
Ocular vasculitis
Oculofacial paralysis
Olfactory nerve disorder
Optic ischaemic neuropathy
Optic neuritis
Optic neuropathy
Optic perineuritis
Overlap syndrome
Palindromic rheumatism
Palisaded neutrophilic granulomatous dermatitis
Palpable purpura
Panencephalitis
Paresis cranial nerve
Pemphigoid
Pemphigus
Pericarditis
Pericarditis lupus
Pericarditis rheumatic
Peripheral spondyloarthritis
Peritonitis lupus
Pernicious anaemia
Pleuroparenchymal fibroelastosis
Polyarteritis nodosa
Polychondritis
Polyglandular autoimmune syndrome type I
Polyglandular autoimmune syndrome type II
Polyglandular autoimmune syndrome type III
Polymyalgia rheumatica
Polymyositis
Polyneuropathy idiopathic progressive
Primary biliary cholangitis
Primary progressive multiple sclerosis
Proctitis ulcerative
Progressive facial hemiatrophy
Progressive multiple sclerosis

Progressive relapsing multiple sclerosis
Psoriasis
Psoriatic arthropathy
Pulmonary fibrosis
Pulmonary renal syndrome
Pulmonary sarcoidosis
Pulmonary vasculitis
Pyoderma gangrenosum
Pyostomatitis vegetans
Radiculitis brachial
Radiologically isolated syndrome
Rasmussen encephalitis
Raynaud's phenomenon
Relapsing multiple sclerosis
Relapsing-remitting multiple sclerosis
Renal arteritis
Renal vasculitis
Retinal occlusive vasculitis
Retinal vasculitis
Reynold's syndrome
Rheumatic brain disease
Rheumatic disorder
Rheumatoid arthritis
Rheumatoid arthritis-associated interstitial lung disease
Rheumatoid bursitis
Rheumatoid lung
Rheumatoid meningitis
Rheumatoid neutrophilic dermatosis
Rheumatoid nodule
Rheumatoid scleritis
Rheumatoid vasculitis
Sarcoidosis
Satoyoshi syndrome
Sclerodactylia
Scleroderma
Scleroderma associated digital ulcer
Scleroderma renal crisis
Secondary progressive multiple sclerosis
Segmented hyalinising vasculitis
Shrinking lung syndrome

Silent thyroiditis
Sjogren's syndrome
SJS-TEN overlap
SLE arthritis
Spondylitis
Spondyloarthropathy
Stevens-Johnson syndrome
Still's disease
Stoma site vasculitis
Subacute cutaneous lupus erythematosus
Subacute inflammatory demyelinating polyneuropathy
Susac's syndrome
Sympathetic ophthalmia
Systemic lupus erythematosus
Systemic lupus erythematosus disease activity index abnormal
Systemic lupus erythematosus disease activity index decreased
Systemic lupus erythematosus disease activity index increased
Systemic lupus erythematosus rash
Systemic scleroderma
Systemic sclerosis pulmonary
Takayasu's arteritis
Terminal ileitis
Testicular autoimmunity
Thromboangiitis obliterans
Thrombocytopenic purpura
Thrombosis with thrombocytopenia syndrome
Thrombotic thrombocytopenic purpura
Tongue paralysis
Toxic epidermal necrolysis
Trigeminal nerve paresis
Trigeminal palsy
Tubulointerstitial nephritis and uveitis syndrome
Tumefactive multiple sclerosis
Type 1 diabetes mellitus
Uhthoff's phenomenon
Ulcerative keratitis
Undifferentiated connective tissue disease
Undifferentiated spondyloarthritis

Urticarial vasculitis
Uveitis
Vaccination site vasculitis
Vaccine associated enhanced disease
Vaccine associated enhanced respiratory disease
Vagus nerve paralysis
Vascular purpura
Vasculitic rash
Vasculitic ulcer
Vasculitis
Vasculitis gastrointestinal
Vasculitis necrotising
VIth nerve paralysis
VIth nerve paresis
Vitiligo
Vocal cord paralysis
Vocal cord paresis
Vogt-Koyanagi-Harada disease
Warm type haemolytic anaemia
XIth nerve paralysis