Statistical Analysis Plan

An open-label trial with TMC278 25 mg q.d. in combination with a background regimen containing 2 nucleoside/nucleotide reverse transcriptase inhibitors in HIV-1 infected subjects, who participated in TMC278 clinical trials

Protocol TMC278-C222; Phase III

TMC278 (Rilpivirine)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ARV	Antiretroviral
CI	Confidence Interval
CM	Concomitant medications
CRF	Case Report Form
DAIDS	Division of AIDS, National Institute of Allergy and Infectious Diseases, USA
DPS	Data Presentation Specifications
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
HIV-1	Human immunodeficiency virus – type 1
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside/Nucleotide Analogue Reverse Transcriptase Inhibitor
LOCF	Last Observation Carried Forward
PI	Protease Inhibitor
q.d.	quaque die; once daily
RNA	Ribonucleic acid
RPV	Rilpivirine
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TMC	Tibotec Medicinal Compound
VF	Virologic Failure

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the Final analysis (Week 360) of safety and efficacy (antiviral activity) for the continued access study TMC278-C222. The data cut-off is 08 February 2018.

1.1. Trial Objectives

The objectives of this study were:

- Primary objective: to provide continued access to RPV for subjects who were randomized and treated with RPV in the Phase IIb (C204) or Phase III trials (C209 and C215).

- Secondary objective: to evaluate the long-term safety and tolerability of RPV 25 mg q.d. in combination with a background regimen containing 2 NRTIs. Available efficacy data will also be collected.

1.2. Trial Design

This was a Phase III, open label, multicenter, roll-over trial to provide continued access to RPV (rilpivirine) in HIV-1 infected subjects who were randomized and treated with RPV in the Phase IIb (C204) or Phase III trials (C209 and C215), and who continued to benefit from their ARV treatment. Information on safety and tolerability was collected. In addition, local information on viral load, ARV resistance and $CD4^+$ count was also collected.

At the baseline visit (roll-over visit), inclusion and exclusion criteria were assessed to confirm eligibility. Once eligibility criteria were met, subjects were to continue treatment with RPV 25 mg q.d. in comination with a background regimen containing 2 NRTIs.

Treatment was to be continued until one of the following criteria were met:

- Virologic failure
- Adverse event (AE)
- Pregnancy
- Loss to follow-up
- Withdrawal of consent
- Subject reached a virologic endpoint
- Sponsor's decision
- Switch to commercially available medication

Visits and assessments were to be performed based on local generally accepted standard of care (see time and events schedule in the protocol). However, it was recommended that visits be planned no less frequently than every 6 months.

Adverse event reporting was limited to:

- AEs considered a least possibly related to RPV
- AEs leading to discontinaution
- serious advese events (SAEs) and pregnancies
- Grade 3/4 rash, irrespective of causality

Other AEs were only collected if required as per local regulation.

1.3. Statistical Hypotheses for Trial Objectives

No formal hypothesis will be tested.

1.4. Sample Size Justification

No sample size calculation was done as this is a continued access single arm trial.

1.5. Randomization and Blinding

Randomization
As this was a continued access single arm trial, randomization procedures were not applicable.

Blinding
Since this was an open label, continued access single-arm trial, blinding procedures were not applicable.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

2.1.1. Trial Phases

Analysis phases are constructed as follows:

Table 1: Analysis Phases for Efficacy and Safety Analysis

Trial phase	Start date	End date
Enrollment	Date of signing informed consent	Day before the start of the treatment phase.
Treatment	Date of the first intake of RPV (in this study)	If the subject *died*: min (date of last RPV intake + 7 days; date of death) Otherwise: minimum of: • date of last RPV intake + 7 days, if missing, max(early withdrawal visit date; discontinuation date)+ 7 days (early withdrawal visit date is from dataset sv and discontinuation date is dsstdtc) • date of last contact (=dm.rfendtc which is the last complete date)
Follow-up (not defined when derived End date is before Start date of this phase)	End date of the Treatment phase + 1 day	If the subject *died*: date of death Otherwise: date of last contact

If the date of first intake of the study medication is missing, this should be substituted by the baseline visit date.

The number of days in the phase is defined as:
relday = visit day – reference day+1 for visits on or after the reference
relday = visit day – reference day for visits before the reference
where the reference day equals the actual start date of intake of RPV.

2.1.2. Analysis Time points

Subjects were to rollover after completion of one of the three parent trials. The baseline visit of this roll-over study coincided with the last visit of the treatment phase of the previous trial. If a subject was deemed eligible to participate in this trial, the subject was to receive trial medication at the baseline visit. After the baseline visit, subjects were to be evaluated as per local regulations, but it was advised that the duration between consecutive visits be no longer than 6 months.

All visits/assessments will be allocated to the following time points as per the table below, based on the number of days in the respective phase, calculated as "assessment date – start date of phase + 1 day" for Treatment and Follow-up phase.

The following time intervals are used for reporting of efficacy data

Table 2: Cut-points and Windows per 24-Week Intervals

Phase	Target day	Analysis time point	Time interval (days)
Treatment	169	Week 24	[1, 252]
	337	Week 48	[253, 420]
	505	Week 72	[421, 588]
	673	Week 96	[589, 756]
	841	Week 120	[757, 924]
	1009	Week 144	[925, 1092]
	1177	Week 168	[1093, 1260]
	1345	Week192	[1261, 1428]
	1513	Week 216	[1429, 1596]
	1681	Week 240	[1597, 1764]
	1849	Week 264	[1765, 1932]
	2017	Week 288	[1933, 2100]
	2185	Week 312	[2101, 2268]
	2353	Week 336	[2269, 2436]
	2521	Week 360	[2437, +∞]
Follow-up	30	Follow-up	[1, +∞]

Only the record prior to or on the first dose closest to target day 1 will be allocated to analysis time point 'Baseline'.

If two visits fall within the same interval, the one closest to the target day is used for the analysis displays and graphics to have only one evaluation per subject per analysis time point. However, all data are presented in the listings. If distances of both visits to the target day are equal, the visit latest in time is used.

Baseline
Baseline refers to the last visit in the parent study, which is the first visit in C222.

2.2. Analysis Sets

Intent-to-treat (ITT) population: the set of all subjects who have taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen.
The intent-to-treat population will be used as primary and only population for all analyses.

2.2.1. Definition of Subgroups

All displays will be created by previous trial (both phase III trials, C209 and C215, will be analyzed together) and overall. The following labels will be used:

- RPV (C204)
- RPV (C209 and C215)
- All subjects

The following subgroups will be defined for **efficacy**:

- Gender
- Race
- Age (<50; >=50 to < 65; >= 65 years at baseline)
- Cumulative adherence based on drug accountability (≤95%, >95%)
- Truvada in background ARV regimen (yes/no)
- Clade

The following subgroups will be defined for **Safety**:

- Truvada in ARV regimen (yes/no)
- Hepatitis B/C Co-infection (based on medical history in parent study)
- Hepatitis B infection (based on medical history in parent study)
- Hepatitis C infection (based on medical history in parent study)
- Age (<50; >=50 to < 65; >= 65 years at baseline)
- CDC classification (based on screening information from the parent study)
- Gender
- Race

3. SUBJECT INFORMATION

3.1. Demographics and Baseline Characteristics

The following parameters will be analyzed:

- Gender (male/female)
- Race (from parent studies)
- Age at baseline
- Age at baseline by categories (<50, ≥50 to <65; ≥65)
- Country/site
- History of Hepatitis B/C
- History of Hepatitis B
- History of Hepatitis C
- Clade

3.2. Disposition Information

Discontinuations, plus reasons for discontinuation will be analyzed:

Summary statistics (count, percentage and rate per 100 person-years) will be provided. Rate per 100 person-years is calculated as (the total number of discontinuations x 100) divided by (the

total number of days summed over all subjects)/365.25. Exact 95% confidence intervals[4] for the number of discontinuation per 100 person-years will also be provided.

3.3. Extent of Exposure

Exposure is defined as the duration of RPV treatment during the active treatment phase (in Days). The extent of exposure will be summarized in years, and the total person-years-of exposure will be provided.

Treatment duration is calculated as follows: *last day of treatment phase – Day of first dose +1*. Note that the above definition implies that drug interruptions are ignored in calculating exposure.

The total person-years-of-exposure will be calculated by taking the sum of the RPV treatment duration (years) over all subjects.

In addition, the proportion of subjects in the study exposed to RPV will be tabulated using 48-week intervals, i.e. based on 1 x 48 weeks (337 days), 2 x 48 weeks (673 days), etc. as cut-points (see Table 2).

3.4. Protocol Deviations

Major protocol deviations will be tabulated and listed.

3.5. Concomitant Medications

Concomitant therapies are defined as therapies listed on the concomitant medications (CM) domain. Concomitant medications are allocated to each phase during which they were administered, based on their start and end dates. For phase allocation, the following rules are applied to deal with (partially) missing start or end dates:

- a start date with the day only missing has the day imputed with the first day of the month;
- a start date with the day and month missing has the day imputed with the 1st of January;
- an entirely missing start date is considered as having started before the study;
- an end date with the day only missing has the day imputed with the last day of the month;
- an end date with the day and month missing has the day imputed with the 31st of December;
- an entirely missing end date is considered as having ended after the study.

Number and percent of subjects per ARV therapy (as started or ongoing at baseline) will be summarized. In addition, all ARV and non-ARV therapies will be listed separately. A separate listing for all subjects who switched ARV therapy during treatment will also be listed. Note: combination drugs will be split into their respective compounds.

3.6. Adherence

Treatment adherence is defined based on drug accountability from tablet counts.

The following parameters are derived over the entire treatment period.

Drug accountability

Amount to be taken = (number of days since start of treatment x number of tablets to be taken per day).

Number of days since start of treatment in C222 is:

- based on last RPV study medication intake date (if available) or, in case subject discontinued and last RPV study medication intake date is missing, discontinuation date
- if not available, the last dispensation visit will be used.

Actual amount taken in C222 = (number of tablets dispensed – number of tablets returned)

Tablets dispensed after or on the date of last dose (based on exposure data) should not be taken into account if there is no information on all dispensed tablets available.

Level of adherence = (actual amount taken / amount to be taken) x 100%
Treatment adherence is defined as:

- adherent: the level of adherence is > 95%
- non-adherent: the level of adherence is ≤ 95%

Additionally, following categories of level of adherence will be defined:

- > 95%
-]80%; 95%]
-]65%; 80%]
-]50%; 65%]
- ≤ 50%

The numbers and percentages of subjects adherent during the trial will be tabulated and descriptive statistics of adherence (%) will be shown.
Interruptions (for AEs) are not to be considered for the calculation of adherence, i.e. they will not be subtracted from the amount to be taken.

Results will be summarized for RPV only.

4. EFFICACY

4.1. Analysis Specifications

4.1.1. Level of Significance

No statistical testing will be done as this is a single arm trial.

4.1.2. Data Handling Rules

Viral load testing was performed locally using several assays. Viral load will be analyzed irrespective of which viral load assay was used (there will be no separate reporting). Regardless

of which assay was used to define response (undetectable)/loss of response (detectable) in the analysis, a cut-off of 50 and 200 copies/mL[2] will be applied.

Imputation of left censored values: 49 copies/mL for values below the detection limit.

Reanalyzed samples will not be used in any of the calculations or summary statistics.

Only samples obtained during the treatment phase will be used for the analyses.

4.2. Efficacy Endpoints

The following viral load parameters will be analyzed:

- **Time to Virologic rebound** defined as the time to (first) HIV-1 RNA ≥50/200 copies/mL. Following rules apply:
    - Virologic rebound needs to be confirmed at 2 consecutive visits with the following exception: loss of response at the last study visit where no confirmation sample is available will be considered as rebound.
    - The analysis will be censored at the time of discontinuation (discontinuation due to ANY reason).
    - This is the time (in days) calculated from baseline until the failure time point. Subjects never losing the acquired response will be censored at the end of the treatment phase.
- **Time to Treatment failure** is defined as
    - The time to virologic rebound (see above) or discontinuation, whichever comes first
    - Subjects who would otherwise had continued will be censored at the end of the treatment phase.
    - This is the time (in days) calculated from baseline until the failure time point. Subjects never losing the acquired response will be censored at the end of the treatment phase.

4.2.1. $CD4^+$ cell count

Actual $CD4^+$ cell count and change in $CD4^+$ cell count (absolute) from baseline up to Week 360 by 24 Week intervals.

Change from baseline in $CD4^+$ count is defined as $CD4^+$ at a given timepoint - baseline $CD4^+$.

- Subjects who discontinued because RPV became commercially available or rolled over to IFD3004 will be censored at that time.
- Subjects who discontinued for any other reason will have their $CD4^+$ values after discontinuation imputed with their baseline value (baseline from roll-over study), thus resulting in a 0 change.
- Intermittently missing values will be imputed using a last observation carried forward approach.

4.2.2. Analysis Methods

For "time to" parameters, Kaplan Meier estimates and 95% CIs will be calculated. Kaplan-Meier curves will be constructed.

In addition, the cumulative number of events (rebound/treatment failure) and the cumulative number per 100 person-years will be summarized by 24-Week treatment period and for the entire treatment period (Week 360 time point). Rate per 100 person-years is calculated as (the number of failures x 100) divided by (the total number of days summed over all subjects)/(365.25). Exact 95% confidence intervals[4] for the number of events per 100 person-years will also be provided.

For continuous parameters, descriptive statistics (n, mean (se), median, and ranges) per time point and graphical display will be presented.

HIV-1 RNA levels will be listed for all subjects with virologic rebound.

5. RESISTANCE DETERMINATIONS

Resistance data will only be analyzed if available for at least 20 subjects. If there are less than 20 subjects, resistance data will be listed. Inclusion of subjects for resistance analysis will solely be based on the availability of post-baseline genotypic data within the treatment phase.

Note: no phenotypic data was collected in this trial.

6. SAFETY

Safety results will be summarized for the Treatment phase only; all safety data (including Follow-up phase) will be included in listings.

6.1. Adverse Events

AE incidence (count, percentage) will be tabulated, overall and by SOC/preferred term.

Overall AE summary tables by preferred term/SOC for serious AEs and pregnancies, AEs leading to discontinuation, AEs at least grade 3, AEs at least grade 4, Grade 3-4 rash, HIV-related AEs and AEs at least possibly related to RPV will be presented throughout the treatment phase only; any AEs in the Follow-up phase will be listed only.

AEs are categorized in different groups of AEs of interest (see Appendix 1).

The different classes of events of interest that will be investigated are the following:

- AEs leading to discontinuation
- Skin events of interest (with subcategories: Rash)
- Neuropsychiatric events of interest (with subcategories: Neurologic events of interest, Psychiatric events of interest). The subcategories are based on System Organ Class.
- Potential QT prolongation-related events
- Hepatic events of interest

- Endocrinology events

Note: the above is based on adverse events of interest analyses in previous Phase 3 studies.

Clinical narratives will be written for: deaths, pregnancies, SAEs at least possibly related to RPV, AEs leading to permanent discontinuation of RPV, grade 3/4 AEs of special interest.

6.2. Clinical Laboratory Tests

6.2.1. Overall Laboratory Safety

Results from local laboratory testing will be included in the analysis. Lab assessments were only collected for following cases: serious AEs, AEs leading to discontinuation, AEs considered at least possibly related to RPV, grade 3/4 rash.

All laboratory values and pregnancy results collected will be listed. Original units will be reported. All lab values will be used, including those from unscheduled laboratory visits and pregnancy results.

Toxicity grades are determined according to the DAIDS grading list (see protocol). More detailed information will be provided in the DPS.

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2. O'Connor J et al 2017 Durability of Viral Suppression with first line anti-retroviral therapy in patients with HIV in the UK: an observational cohort study; Lancet HIV. 2017 Jul; 4(7): e295–e302.
3. Bennett DE, Camacho RJ, Otelea D, Kuritzkes DR, Fleury H, et al. 2009 Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2009 Update. PLoS ONE 4(3): e4724. doi:10.1371/journal.pone.000472
4. Ulm K: A simple method to calculate the confidence interval of a standardized mortality ratio (SMR); Am J Epidemiol 1990; 131(2): 373-5.

APPENDIX 1: ADVERSE EVENTS OF INTEREST

AEDECOD	Category	Subcategory
17-HYDROXYPROGESTERONE INCREASED	ENDOCRINE	
ACTH STIMULATION TEST ABNORMAL	ENDOCRINE	
ADRENAL ADENOMA	ENDOCRINE	
ADRENOCORTICAL INSUFFICIENCY CHRONIC	ENDOCRINE	
AMENORRHOEA	ENDOCRINE	
BLOOD ALDOSTERONE DECREASED	ENDOCRINE	
BLOOD CORTISOL ABNORMAL	ENDOCRINE	
BLOOD CORTISOL DECREASED	ENDOCRINE	
BLOOD CORTISOL INCREASED	ENDOCRINE	
DEHYDROEPIANDROSTERONE DECREASED	ENDOCRINE	
DYSFUNCTIONAL UTERINE BLEEDING	ENDOCRINE	
HAIR GROWTH ABNORMAL	ENDOCRINE	
HYPERTRICHOSIS	ENDOCRINE	
HYPOGONADISM	ENDOCRINE	
HYPOTRICHOSIS	ENDOCRINE	
MENOMETRORRHAGIA	ENDOCRINE	
MENORRHAGIA	ENDOCRINE	
MENSTRUAL DISORDER	ENDOCRINE	
MENSTRUATION DELAYED	ENDOCRINE	
MENSTRUATION IRREGULAR	ENDOCRINE	
METRORRHAGIA	ENDOCRINE	
OVARIAN CYST	ENDOCRINE	
PAROVARIAN CYST	ENDOCRINE	
PIGMENTATION DISORDER	ENDOCRINE	
POLYMENORRHOEA	ENDOCRINE	
POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME	ENDOCRINE	
PROGESTERONE ABNORMAL	ENDOCRINE	
PROGESTERONE INCREASED	ENDOCRINE	
SKIN DISCOLOURATION	ENDOCRINE	
SKIN HYPERPIGMENTATION	ENDOCRINE	
SKIN HYPOPIGMENTATION	ENDOCRINE	
ACUTE HEPATIC FAILURE	HEPATOBILIARY	
ALANINE AMINOTRANSFERASE ABNORMAL	HEPATOBILIARY	
ALANINE AMINOTRANSFERASE INCREASED	HEPATOBILIARY	
ASPARTATE AMINOTRANSFERASE ABNORMAL	HEPATOBILIARY	
ASPARTATE AMINOTRANSFERASE INCREASED	HEPATOBILIARY	
BILIRUBIN CONJUGATED INCREASED	HEPATOBILIARY	
BILIRUBINURIA	HEPATOBILIARY	
BIOPSY LIVER	HEPATOBILIARY	
BLOOD ALKALINE PHOSPHATASE INCREASED	HEPATOBILIARY	
BLOOD BILIRUBIN INCREASED	HEPATOBILIARY	
BLOOD BILIRUBIN UNCONJUGATED INCREASED	HEPATOBILIARY	

BLOOD LACTATE DEHYDROGENASE INCREASED	HEPATOBILIARY
CHOLELITHIASIS	HEPATOBILIARY
CYTOLYTIC HEPATITIS	HEPATOBILIARY
GAMMA-GLUTAMYLTRANSFERASE INCREASED	HEPATOBILIARY
HEPATIC CIRRHOSIS	HEPATOBILIARY
HEPATIC ENZYME ABNORMAL	HEPATOBILIARY
HEPATIC ENZYME INCREASED	HEPATOBILIARY
HEPATIC FAILURE	HEPATOBILIARY
HEPATIC FUNCTION ABNORMAL	HEPATOBILIARY
HEPATIC FUNCTION ABNORMAL NOS	HEPATOBILIARY
HEPATIC STEATOSIS	HEPATOBILIARY
HEPATITIS	HEPATOBILIARY
HEPATITIS ACUTE	HEPATOBILIARY
HEPATITIS B	HEPATOBILIARY
HEPATITIS C	HEPATOBILIARY
HEPATOBILIARY DISEASE	HEPATOBILIARY
HEPATOMEGALY	HEPATOBILIARY
HEPATOSPLENOMEGALY	HEPATOBILIARY
HEPATOSPLENOMEGALY NOS	HEPATOBILIARY
HEPATOTOXICITY	HEPATOBILIARY
HEPATOTOXICITY NOS	HEPATOBILIARY
HYDROCHOLECYSTIS	HEPATOBILIARY
HYPERBILIRUBINAEMIA	HEPATOBILIARY
HYPERBILIRUBINEMIA	HEPATOBILIARY
HYPERTRANSAMINASAEMIA	HEPATOBILIARY
JAUNDICE	HEPATOBILIARY
JAUNDICE NOS	HEPATOBILIARY
LIVER DISORDER	HEPATOBILIARY
LIVER FATTY	HEPATOBILIARY
LIVER FUNCTION TEST ABNORMAL	HEPATOBILIARY
LIVER PALPABLE SUBCOSTAL	HEPATOBILIARY
TRANSAMINASES INCREASED	HEPATOBILIARY
URINE BILIRUBIN INCREASED	HEPATOBILIARY
YELLOW SKIN	HEPATOBILIARY
ABNORMAL BEHAVIOUR	NEUROPSYCH
ABNORMAL DREAMS	NEUROPSYCH
ACUTE PSYCHOSIS	NEUROPSYCH
ADJUSTMENT DISORDER	NEUROPSYCH
ADJUSTMENT DISORDER NOS	NEUROPSYCH
ADJUSTMENT DISORDER WITH ANXIETY	NEUROPSYCH
ADJUSTMENT DISORDER WITH DEPRESSED MOOD	NEUROPSYCH
ADJUSTMENT DISORDER WITH MIXED ANXIETY AND DEPRESSED MOOD	NEUROPSYCH
AFFECT LABILITY	NEUROPSYCH
AFFECTIVE DISORDER	NEUROPSYCH

AGGRESSION	NEUROPSYCH
AGITATION	NEUROPSYCH
AGORAPHOBIA	NEUROPSYCH
ALCOHOL ABUSE	NEUROPSYCH
ALCOHOL POISONING	NEUROPSYCH
ALCOHOL WITHDRAWAL SYNDROME	NEUROPSYCH
ALCOHOLISM	NEUROPSYCH
AMNESIA	NEUROPSYCH
ANGER	NEUROPSYCH
ANHEDONIA	NEUROPSYCH
ANXIETY	NEUROPSYCH
ANXIETY DISORDER	NEUROPSYCH
APATHY	NEUROPSYCH
ATTENTION DEFICIT/HYPERACTIVITY DISORDER	NEUROPSYCH
AUTONOMIC NERVOUS SYSTEM IMBALANCE	NEUROPSYCH
BALANCE DISORDER	NEUROPSYCH
BALANCE IMPAIRED	NEUROPSYCH
BALANCE IMPAIRED NOS	NEUROPSYCH
BIPOLAR DISORDER	NEUROPSYCH
BIPOLAR I DISORDER	NEUROPSYCH
BOREDOM	NEUROPSYCH
BRADYPHRENIA	NEUROPSYCH
BRUXISM	NEUROPSYCH
CATATONIA	NEUROPSYCH
CLAUSTROPHOBIA	NEUROPSYCH
CLUSTER HEADACHE	NEUROPSYCH
COGNITIVE DISORDER	NEUROPSYCH
COMPLETED SUICIDE	NEUROPSYCH
CONCENTRATION IMPAIRED	NEUROPSYCH
CONFUSIONAL STATE	NEUROPSYCH
CONVERSION DISORDER	NEUROPSYCH
COORDINATION ABNORMAL	NEUROPSYCH
CRANIAL NEUROPATHY	NEUROPSYCH
DECREASED ACTIVITY	NEUROPSYCH
DELIRIUM	NEUROPSYCH
DELUSION	NEUROPSYCH
DEPRESSED LEVEL OF CONSCIOUSNESS	NEUROPSYCH
DEPRESSED MOOD	NEUROPSYCH
DEPRESSION	NEUROPSYCH
DEPRESSION AGGRAVATED	NEUROPSYCH
DEPRESSIVE SYMPTOM	NEUROPSYCH
DISORIENTATION	NEUROPSYCH
DISSOCIATION	NEUROPSYCH
DISTRACTIBILITY	NEUROPSYCH
DISTURBANCE IN ATTENTION	NEUROPSYCH

DIZZINESS	NEUROPSYCH
DRUG DEPENDENCE	NEUROPSYCH
DYSPHORIA	NEUROPSYCH
DYSSOMNIA	NEUROPSYCH
DYSTHYMIC DISORDER	NEUROPSYCH
EARLY MORNING AWAKENING	NEUROPSYCH
EMOTIONAL DISORDER	NEUROPSYCH
EMOTIONAL DISTRESS	NEUROPSYCH
EUPHORIC MOOD	NEUROPSYCH
HALLUCINATION	NEUROPSYCH
HALLUCINATION, AUDITORY	NEUROPSYCH
HALLUCINATION, VISUAL	NEUROPSYCH
HALLUCINATIONS, MIXED	NEUROPSYCH
HEAD DISCOMFORT	NEUROPSYCH
HEADACHE	NEUROPSYCH
HEADACHE NOS AGGRAVATED	NEUROPSYCH
HEMICEPHALALGIA	NEUROPSYCH
HOMICIDAL IDEATION	NEUROPSYCH
HYPERKINESIA	NEUROPSYCH
HYPERSOMNIA	NEUROPSYCH
HYPOMANIA	NEUROPSYCH
INITIAL INSOMNIA	NEUROPSYCH
INSOMNIA	NEUROPSYCH
INSOMNIA EXACERBATED	NEUROPSYCH
IRRITABILITY	NEUROPSYCH
LETHARGY	NEUROPSYCH
LIBIDO DECREASED	NEUROPSYCH
LIBIDO DISORDER	NEUROPSYCH
LIBIDO INCREASED	NEUROPSYCH
LISTLESS	NEUROPSYCH
LOSS OF LIBIDO	NEUROPSYCH
MAJOR DEPRESSION	NEUROPSYCH
MALE ORGASMIC DISORDER	NEUROPSYCH
MANIA	NEUROPSYCH
MEMORY IMPAIRMENT	NEUROPSYCH
MENTAL DISORDER	NEUROPSYCH
MENTAL IMPAIRMENT	NEUROPSYCH
MENTAL STATUS CHANGES	NEUROPSYCH
MIDDLE INSOMNIA	NEUROPSYCH
MONONEUROPATHY	NEUROPSYCH
MOOD ALTERED	NEUROPSYCH
MOOD SWINGS	NEUROPSYCH
NEGATIVE THOUGHTS	NEUROPSYCH
NERVOUSNESS	NEUROPSYCH
NIGHTMARE	NEUROPSYCH

NIGHTMARES	NEUROPSYCH
ORGASM ABNORMAL	NEUROPSYCH
PANIC ATTACK	NEUROPSYCH
PANIC DISORDER	NEUROPSYCH
PARAESTHESIA CIRCUMORAL	NEUROPSYCH
PARANOIA	NEUROPSYCH
PERSONALITY DISORDER	NEUROPSYCH
PHOBIA	NEUROPSYCH
PHOTOPHOBIA	NEUROPSYCH
POOR QUALITY SLEEP	NEUROPSYCH
POST-TRAUMATIC STRESS DISORDER	NEUROPSYCH
PSYCHIATRIC INVESTIGATION	NEUROPSYCH
PSYCHOGENIC ERECTILE DYSFUNCTION	NEUROPSYCH
PSYCHOLOGICAL FACTOR AFFECTING MEDICAL CONDITION	NEUROPSYCH
PSYCHOMOTOR HYPERACTIVITY	NEUROPSYCH
PSYCHOTIC DISORDER	NEUROPSYCH
PSYCHOTIC DISORDER DUE TO A GENERAL MEDICAL CONDITION	NEUROPSYCH
RESTLESS LEGS SYNDROME	NEUROPSYCH
RESTLESSNESS	NEUROPSYCH
SEASONAL AFFECTIVE DISORDER	NEUROPSYCH
SEDATION	NEUROPSYCH
SENSATION OF PRESSURE IN EAR	NEUROPSYCH
SENSE OF OPPRESSION	NEUROPSYCH
SLEEP DISORDER	NEUROPSYCH
SLEEP DISORDER NOS	NEUROPSYCH
SLEEP PHASE RHYTHM DISTURBANCE	NEUROPSYCH
SLUGGISHNESS	NEUROPSYCH
SOCIAL PHOBIA	NEUROPSYCH
SOMATOFORM DISORDER	NEUROPSYCH
SOMNOLENCE	NEUROPSYCH
SOPOR	NEUROPSYCH
STRESS	NEUROPSYCH
STRESS SYMPTOMS	NEUROPSYCH
SUBSTANCE ABUSE	NEUROPSYCH
SUICIDAL IDEATION	NEUROPSYCH
SUICIDE ATTEMPT	NEUROPSYCH
TENSION	NEUROPSYCH
UVEITIS	NEUROPSYCH
VERTIGO	NEUROPSYCH
VISION BLURRED	NEUROPSYCH
VISUAL DISTURBANCE	NEUROPSYCH
CARDIAC ARREST	QT PROLONGING EFF
CARDIAC DEATH	QT PROLONGING EFF
CARDIAC FIBRILLATION	QT PROLONGING EFF
CARDIO-RESPIRATORY ARREST	QT PROLONGING EFF

ELECTROCARDIOGRAM QT INTERVAL ABNORMAL	QT PROLONGING EFF	
ELECTROCARDIOGRAM QT PROLONGED	QT PROLONGING EFF	
ELECTROCARDIOGRAM REPOLARISATION ABNORMALITY	QT PROLONGING EFF	
ELECTROCARDIOGRAM U-WAVE ABNORMALITY	QT PROLONGING EFF	
ELECTROCARDIOGRAM U-WAVE BIPHASIC	QT PROLONGING EFF	
LONG QT SYNDROME	QT PROLONGING EFF	
LONG QT SYNDROME CONGENITAL	QT PROLONGING EFF	
LOSS OF CONSCIOUSNESS	QT PROLONGING EFF	
SUDDEN CARDIAC DEATH	QT PROLONGING EFF	
SUDDEN DEATH	QT PROLONGING EFF	
SYNCOPE	QT PROLONGING EFF	
TORSADE DE POINTES	QT PROLONGING EFF	
VENTRICULAR ARRHYTHMIA	QT PROLONGING EFF	
VENTRICULAR FIBRILLATION	QT PROLONGING EFF	
VENTRICULAR FLUTTER	QT PROLONGING EFF	
VENTRICULAR TACHYARRHYTHMIA	QT PROLONGING EFF	
VENTRICULAR TACHYCARDIA	QT PROLONGING EFF	
DERMATITIS CONTACT	SKIN	Dermatitis contact
URTICARIA CONTACT	SKIN	Dermatitis contact
DERMATITIS	SKIN	Dermatitis/Eczema
DERMATITIS ATOPIC	SKIN	Dermatitis/Eczema
DERMATITIS EXFOLIATIVE	SKIN	Dermatitis/Eczema
DERMATITIS NOS	SKIN	Dermatitis/Eczema
ECZEMA	SKIN	Dermatitis/Eczema
ECZEMA NUMMULAR	SKIN	Dermatitis/Eczema
SEBORRHOEIC DERMATITIS	SKIN	Dermatitis/Eczema
SKIN INFLAMATION	SKIN	Dermatitis/Eczema
SKIN INFLAMMATION	SKIN	Dermatitis/Eczema
SKIN INFLAMMATION NOS	SKIN	Dermatitis/Eczema
EYE SWELLING	SKIN	Oedema
LARYNGEAL OEDEMA	SKIN	Oedema
PHARYNGEAL OEDEMA	SKIN	Oedema
BLISTER	SKIN	Other
CHLOASMA	SKIN	Other
DESQUAMATION	SKIN	Other
EOSINOPHILIC PUSTULAR FOLLICULITIS	SKIN	Other
ERYTHEMA NODOSUM	SKIN	Other
INFECTED SKIN ULCER	SKIN	Other
LIP BLISTER	SKIN	Other
LIP ULCERATION	SKIN	Other
NEURODERMATITIS	SKIN	Other
PENILE ULCERATION	SKIN	Other
PHOTOSENSITIVITY REACTION	SKIN	Other
PHOTOSENSITIVITY REACTION NOS	SKIN	Other
POLYMORPHIC LIGHT ERUPTION	SKIN	Other

SCROTAL ULCER	SKIN	Other
SEBORRHOEA	SKIN	Other
SKIN DESQUAMATION	SKIN	Other
SKIN DESQUAMATION NOS	SKIN	Other
SKIN EXFOLIATION	SKIN	Other
SKIN ULCER	SKIN	Other
SKIN ULCERATION	SKIN	Other
ANGIONEUROTIC OEDEMA	SKIN	Rash
DERMATITIS ALLERGIC	SKIN	Rash
DERMATITIS MEDICAMENTOSA	SKIN	Rash
DRUG ERUPTION	SKIN	Rash
DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS	SKIN	Rash
ERYTHEMA	SKIN	Rash
ERYTHEMA GENERALISED	SKIN	Rash
ERYTHEMA INDURATUM	SKIN	Rash
ERYTHEMA OF EYELID	SKIN	Rash
EXANTHEM	SKIN	Rash
EXFOLIATIVE RASH	SKIN	Rash
EYELID OEDEMA	SKIN	Rash
FACE OEDEMA	SKIN	Rash
GENERALISED ERYTHEMA	SKIN	Rash
GENITAL ERYTHEMA	SKIN	Rash
GENITAL RASH	SKIN	Rash
PERIORBITAL OEDEMA	SKIN	Rash
PRURIGO	SKIN	Rash
PRURITUS	SKIN	Rash
RASH	SKIN	Rash
RASH ERYTHEMATOUS	SKIN	Rash
RASH FOLLICULAR	SKIN	Rash
RASH GENERALISED	SKIN	Rash
RASH MACULAR	SKIN	Rash
RASH MACULO-PAPULAR	SKIN	Rash
RASH MORBILLIFORM	SKIN	Rash
RASH NOS	SKIN	Rash
RASH PAPULAR	SKIN	Rash
RASH PRURITIC	SKIN	Rash
RASH PUSTULAR	SKIN	Rash
RASH SCALY	SKIN	Rash
RASH URTICARIA-LIKE	SKIN	Rash
SKIN REACTION	SKIN	Rash
SKIN TOXICITY	SKIN	Rash
SWELLING FACE	SKIN	Rash
TOXIC SKIN ERUPTION	SKIN	Rash
URTICARIA	SKIN	Rash
URTICARIA CHRONIC	SKIN	Rash

URTICARIA GENERALISED	SKIN	Rash
URTICARIA LOCALISED	SKIN	Rash
URTICARIA NOS	SKIN	Rash
URTICARIA PAPULAR	SKIN	Rash
DERMATITIS BULLOUS	SKIN	Rash vesicular
ERYTHEMA MULTIFORME	SKIN	Rash vesicular
RASH VESICULAR	SKIN	Rash vesicular
STEVENS-JOHNSON SYNDROME	SKIN	Rash vesicular