Janssen Pharmaceutical K.K. *

Statistical Analysis Plan for Primary Analysis, and Final Analysis

A Phase 2a, Multicenter, Open-label Study to Investigate the Safety, Pharmacokinetics, and Efficacy of Combination Treatment of AL-335, Odalasvir, and Simeprevir in Japanese Subjects With Chronic Hepatitis C Genotype 1 or 2 Virus Infection, With or Without Compensated Cirrhosis who are Direct-acting Antiviral Treatment-naïve

Protocol 64294178HPC2003; Phase 2a

AL-335, Odalasvir, TMC435(simeprevir)

*This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K.

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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

ADaM	Analysis Data Model
AE	Adverse Event
BMI	Body Mass Index
CFB	Change from Baseline
CTP	Clinical Trial Protocol
DAA	Direct-Acting Antivirals
DRC	Data Review Committee
ECG	Electrocardiogram
ECHO	Echocardiogram / Echocardiography
eCRF	Electronic Case Report Form
EOT	End Of Treatment
HCV	Hepatitis C Virus
IA	Interim Analysis
ITT	Intent-To-Treat
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
NAP	Not Applicable
ODV	Odalasvir
PT	Preferred Term
QD	Quaque Die, Once Daily
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI	Standard International
SMV	Simeprevir
SOC	System Organ Class
WHO	World Health Organization

1. INTRODUCTION

This 64294178HPC2003 Statistical Analysis Plan (SAP) covers Cut-Off Analysis, Primary Analysis and Final Analysis. It contains definitions of analysis sets, derived variables and statistical methods for the analysis. Separate document for DPS is also provided. A separate SAP was written for the Data Review Committee (DRC) analyses.

Please refer to the study protocol for the background for the study.

1.1. Trial Objectives

Primary Objectives

- To evaluate the safety and tolerability of a combination treatment of AL-335, ODV, and SMV for 8 weeks in DAA-naïve Japanese subjects with genotype 1 or 2 chronic HCV infection without cirrhosis and for 12 weeks in DAA-naïve Japanese subjects with genotype 1 or 2 chronic HCV infection with compensated cirrhosis.

Secondary Objectives

- To evaluate the PK of AL-335 (and metabolites), ODV, and SMV in plasma in Japanese subjects with genotype 1 or 2 chronic HCV infection with or without compensated cirrhosis who are DAA-naïve.
- To evaluate the efficacy, ie, SVR4, SVR12, and SVR24, of a combination treatment with AL-335, ODV, and SMV for 8 weeks in DAA-naïve Japanese subjects with genotype 1 or 2 chronic HCV infection without cirrhosis and for 12 weeks in DAA-naïve Japanese subjects with genotype 1 or 2 chronic HCV infection with compensated cirrhosis.
- To evaluate on-treatment viral kinetics in an 8 or 12-week treatment regimen containing AL-335, ODV, and SMV in subjects who are DAA- naïve.
- To evaluate the incidence of on-treatment failure during an 8 or 12-week treatment regimen containing AL-335, ODV, and SMV in subjects who are DAA-naïve.
- To evaluate the incidence of viral relapse after an 8 or 12-week treatment regimen containing AL-335, ODV, and SMV in subjects who are DAA-naïve.

Exploratory Objectives

- To explore relationships of exposure of AL-335 (and metabolites), ODV, and SMV with SVR and safety.
- To evaluate the impact of the patient and disease characteristics at baseline on SVR, including but not limited to prior treatment history, IL28B genotype, presence of cirrhosis, HCV RNA level, and HCV geno/subtype.
- To evaluate the impact of the presence of HCV NS3/4A, NS5A, and/or NS5B polymorphisms at baseline on treatment outcome.
- To assess the emergence of resistant variants in subjects not achieving SVR.

1.2. Trial Design

This is a Phase 2a, multicenter, open-label study. It consists of a 6-week Screening Period, followed by the 8-week or 12-week Treatment Period, and the 24-week Posttreatment Follow-up Period.

Approximately 20 DAA-naïve chronic HCV genotype 1 or 2-infected subjects without cirrhosis will be assigned to Cohort 1, and approximately 20 DAA-naïve chronic HCV genotype 1 or 2-infected subjects with compensated cirrhosis will be assigned to Cohort 2.

- Cohort 1 (N=20, chronic hepatitis C without cirrhosis):

  AL-335 800 mg once daily + ODV 25 mg once daily + SMV 75 mg once daily for 8 weeks
- Cohort 2 (N=20, chronic hepatitis C with compensated cirrhosis):

  AL-335 800 mg once daily + ODV 25 mg once daily + SMV 75 mg once daily for 12 weeks

To conduct this study carefully in light of securing subjects' safety, after 6 subjects in Cohort 1 completed the Week 4 visit, DRC will review all available relevant safety data to make a decision about start of dosing in Cohort 2.

Further trial design details are available in the protocol.

1.2.1. Endpoints

Primary Endpoint

Safety data, including but not limited to adverse events (AEs), 12-lead electrocardiograms (ECGs), echocardiograms, and clinical laboratory results (including chemistry, hematology, and urine).

Secondary Endpoints

- PK parameters for AL-335 (and metabolites), ODV, and SMV in plasma
- The proportion of subjects who have an SVR4, SVR12, and SVR24
- The proportion of subjects with viral relapse
- The proportion of subjects with on-treatment failure
- The proportion of subjects with on-treatment virologic response:
  - HCV RNA not detected
  - HCV RNA <LLOQ
- Time to achieve HCV RNA not detected or HCV RNA <LLOQ

Exploratory Endpoints

- The effect of the presence or absence at baseline of HCV NS5A, NS5B, and/or NS3/4A polymorphisms on treatment outcome

- The changes in the HCV NS3/4A, NS5A and/or NS5B sequences in subjects not achieving SVR
- Impact of baseline condition on SVR (including but not limited to prior treatment history, IL28B genotype, presence of cirrhosis, HCV RNA level, and HCV geno/subtype)

1.3. Statistical Hypotheses for Trial Objectives

The study is hypothesis-generating. No formal hypothesis will be tested

1.4. Sample Size Justification

Since this is an exploratory study, no formal sample size calculation has been performed.

With a total sample size of 40 subjects, the probability to observe an AE with an incidence of 10.0% is 99.0%. The probability to observe an AE with an incidence of 1.0%, 2.5%, and 5.0% is 33.0%, 64.0%, and 87.0%, respectively. With 20 subjects per cohort, the probability to observe an AE with an incidence of 10.0% is 88.0%. The probability to observe an AE with an incidence of 1.0%, 2.5%, and 5.0% is 18.0%, 40.0%, and 64.0%, respectively in a cohort.

With an expected SVR rate of 90.0%, and 40 subjects in 2 cohorts combined, the corresponding 95%, 2-sided confidence interval (CI) is 76.3% to 97.2%. With 95.0% SVR, the corresponding 95% CI ranges from 83.1% to 99.4%. With an expected SVR rate of 90.0%, and 20 subjects per cohort, the corresponding 95%, 2-sided CI is 68.3% to 98.8%. With 95.0% SVR, the corresponding 95% CI ranges from 75.1% to 99.9% in a cohort.

Therefore, a total sample size of approximately 40 subjects is considered sufficient to explore the safety and efficacy of the combination regimen consisting of AL-335, ODV, and SMV in this study from a clinical point of view.

1.5. Randomization and Blinding

Randomization and Blinding will not be used as this is an open-label study. Subjects will be assigned to a treatment cohort based on the presence or absence of cirrhosis.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows and Phase Definition

Phases will be constructed as indicated in Table 1 and Table 2.

Table 1: Phase Definition Part 1

Cohort	W-6	D1	D2	D3	W1	W2	W3	W4	W6	W8	-	-	W4 FU	W8 FU	W12 FU	W18 FU	W24 FU
Cohort 1	Scr.	AL-335 + ODV + SMV 8 weeks									-	-	Follow up				
Weeks	W-6	D1	D2	D3	W1	W2	W3	W4	W6	W8	W10	W12	W4 FU	W8 FU	W12 FU	W18 FU	W24 FU
Cohort 2	Scr.	AL-335 + ODV + SMV 12 weeks											Follow up				

Table 2: Phase Definition Part 2

Trial phase	Start date	End date
Screening (phase 0)	Minimum of Date of signing the informed consent and Date of the first screening visit	1 day before first study drug administration
Treatment (phase 1)	Date of first study drug administration	Date of last study drug intake + 3 days
Follow-up (phase 2)	Phase 1 end date +1 day	Trial termination date (date of last contact)

Date of First Study Drug Administration: In the above computations, missing data for first study drug intake may be imputed as the date of baseline visit.

Date of Last Study Drug Administration: In the above computations, missing data for last study drug intake may be imputed for cut-off analysis and subjects discontinued as follows:

1. Cut-off analyses: Date of Last Study Drug Intake = Min (Data cutoff date, Date of baseline visit + 8 or 12 weeks depending on cohort).
2. Date of Last Study Drug Intake =
   a. Date of the early treatment withdrawal visit, if nonmissing otherwise
   b. Date of 1st available Follow-up visit – 28, if nonmissing otherwise
   c. Date of last contact.

Reference date is defined as:

- Screening and Treatment Phases: Reference date = Date of first study drug intake (if nonmissing), otherwise date of baseline visit.
- Follow-up Phase: Reference date = Start Date of follow-up phase.

The number of days in the phase (Relative day) is defined as:

- Visits on or after the reference date: Relative day = visit date – reference date+1
- Visits before the reference date: Relative day = visit date – reference date
- Actual EOT visit is defined as the last visit in the Treatment phase.

All visits (regardless of the investigated parameter) will be allocated to analysis time points based on the number of days in phase (relative day) as indicated in Table 3.

Table 3: Visit Windows

Trial phase	Target day	Analysis time point (numeric version)	Analysis time point	Time interval (Relative day)
Cohort 1				
Screening phase	+ ∞	-1	Screening	<0
Treatment phase	1	0	Baseline[a]	<=1
	2	0.2	Day 2	[2,2]
	3	0.3	Day 3	[3,5]
	7	1	Week 1	[6,11]
	14	2	Week 2	[12,18]
	21	3	Week 3	[19,25]
	28	4	Week 4	[26,35]
	42	6	Week 6	[36,49]
	56	8	Week 8	[50, + ∞]
	last visit while on study therapy or within 3 days after the day of last dose	999	EOT	
Follow-up phase	25	16	Follow-Up Week 4	[1,39]
	53	20	Follow-Up Week 8	[40,67]
	81	24	Follow-Up Week 12	[68,102]
	123	30	Follow-Up Week 18	[103,144]
	165	36	Follow-Up Week 24	[145, + ∞]
Cohort 2				
Screening phase	-∞	-1	Screening	<0
Treatment phase	1	0	Baseline[a]	<=1
	2	0.2	Day 2	[2,2]
	3	0.3	Day 3	[3,5]
	7	1	Week 1	[6,11]
	14	2	Week 2	[12,18]
	21	3	Week 3	[19,25]
	28	4	Week 4	[26,35]
	42	6	Week 6	[36,49]
	56	8	Week 8	[50,63]
	70	10	Week 10	[64,77]
	84	12	Week 12	[78, + ∞]
	last visit while on study therapy or within 3 days after the day of last dose	999	EOT	
Follow-up phase	25	16	Follow-Up Week 4	[1,39]
	53	20	Follow-Up Week 8	[40,67]
	81	24	Follow-Up Week 12	[68,102]
	123	30	Follow-Up Week 18	[103,144]
	165	36	Follow-Up Week 24	[145, + ∞]

Note:

Target day in follow up phase equals target day in the protocol minus 3 days due to definition of start of follow-up phase.

If two visits fall within the same interval, the last measurement within the interval will be used for descriptive statistics/tabulations per time point and graphics in order to have only one evaluation per subject per analysis time point. If two measurements occur on the same day, the measurement with highest sequence number will be used. Listings will include all values.

2.2. Pooling Algorithm for Analysis Centers

No pooling of analysis subcenters will be performed in this study.

2.3. Analysis Sets

Safety Analysis Set: All enrolled subjects who received at least 1 dose of study drug (AL-335, ODV, or SMV).

Full Analysis Set (FAS): All enrolled subjects who received at least 1 dose of study drug (AL-335, ODV, or SMV) and have at least 1 postbaseline efficacy measurement.

Non-VF Excluded Set: All FAS subjects excluding subjects with early treatment discontinuation due to nonvirologic reasons or missing data at SVR4, SVR12, or SVR24 time points.

All analyses except for efficacy, and virology analyses will be done on safety analysis set. The efficacy analyses will be performed on full analysis set. Selected virology analyses will be using non-VF excluded set as needed. Demographic and baseline characteristics should be done on the safety.

2.4. Definition of Subgroups

The subgroups will be used to perform analyses on efficacy endpoints are:

- Age category [≤65; >65]
- BMI [<25; ≥25]
- IL28B genotype (CC, CT, TT); and also (CC, non-CC)
- Gender (male, female)
- HCV geno/subtype (1a, 1b, 1other, 1a with Q80K, 1a without Q80K, 2a, 2b, 2c, 2other)
- baseline HCV RNA categories (<6,000,000 IU/mL, ≥6,000,000 IU/mL)

The subgroups will be used to perform analyses on safety endpoints are:

- Age category [≤65; >65]
- BMI [<25; ≥25]
- Gender (male, female)

3. SUBJECT INFORMATION

3.1. Demographics and Baseline Characteristics

Descriptive statistics or tabulation will be provided, in addition to listings, for the following parameters:

Demographic parameters

- Gender (male, female)

- Age at screening (years)
- Age at screening (years, categories: ≤45; >45 - ≤65; >65)
- Race (Asian)
- Ethnicity (Not Hispanic or Not Latino)
- Weight at baseline (kg)
- BMI at baseline = weight (at baseline, in kg)/ (height (at screening, in meters))^2, rounded to 1 decimal (although available in the raw data, BMI will be recalculated from weight and height)
- BMI at baseline (categories: <25, 25-<30, ≥30)

Baseline disease characteristics

- baseline HCV RNA (original and $\log_{10}$ units)
- baseline HCV RNA categories (<6,000,000 IU/mL, ≥6,000,000 IU/mL)
- HCV geno/subtype 1a, 1b, 1other, 1a with Q80K, 1a without Q80K, 2a, 2b, 2c, 2other
- Prior IFN with or without RBV taken (Yes or No)
- IL28B subtype (CC, CT, TT)
- For subjects with Fibroscan Results:
  - Fibroscan Metavir Fibrosis Result (kPa)
  - Fibroscan Metavir Fibrosis stage (F0/F1, F2, F3, F4)
- For subjects with Biopsy Results (Each subject has either Metavir or Ishak scoring):
  - Biopsy Metavir Fibrosis stage (F0/F1, F2, F3, F4)
  - Metavir Inflammation grade (A0, A1, A2, A3)
  - Biopsy Ishak Fibrosis stage (0, 1, 2, 3, 4, 5, 6)
  - Ishak Inflammation grade (1-3, 4-8, 9-12, 13-18)
- Time since diagnosis (years) (= (baseline date – date of diagnosis + 1)/365.25, rounded to 1 decimal)

3.2. Disposition Information

Tabulations will be provided for the following disposition information:

- Number of subjects screened, enrolled and treated
- Number of subjects with a visit per analysis time point
- Number of subjects prematurely discontinuing any single study medication and the reason for discontinuation (obtained from the treatment disposition page of the electronic case report form [eCRF])

- Number of subjects prematurely discontinuing the trial and the reason for discontinuation. Reasons for discontinuation are obtained from the trial disposition page of the eCRF.

3.3. Treatment Adherence

For each of the three drugs (AL-335, Odalasvir, SMV), the actual amount (actual dose over actual treatment duration) of study drug relative to the planned cumulative total dose (planned dose over planned duration) will be summarized.

For each drug, the number (%) of subjects with ≤3 and >3 consecutive days of dose interruption will be tabulated. The number of subjects without a dose interruption will also be tabulated. Summary statistics for the total number of days of dose interruption for subjects with at least one day of dose interruption will also be tabulated. Further, for each drug, the number (%) of subjects with ≤3, 4 - ≤6, and >6 cumulative days of dose interruption will be tabulated.

3.4. Extent of Exposure

Treatment duration (in weeks) is derived as follows for each of the three drugs (AL-335, Odalasvir, SMV):

- (Last date of exposure – first date of exposure + 1) / 7

Note: treatment interruptions will not be taken into account for the above definition.

Treatment duration and total dose received will be summarized descriptively by treatment cohort. Treatment duration for subjects who did not complete treatment will also be summarized descriptively by treatment cohort.

3.5. Protocol Deviations

All major protocol deviations will be tabulated. Additionally, all protocol deviations (major and minor) will be listed. Major protocol deviations that may affect the assessment of efficacy will be flagged in the listing.

3.6. Prior and Concomitant Medications

Prior medications will be tabulated by treatment cohort. Concomitant medications will be tabulated by treatment cohort and by phase. Concomitant medications are allocated to phases based on their start and stop date. The concomitant medications will be allocated to a phase during which they were applied. A concomitant medication can be allocated to more than one phase.

Incomplete dates (ie, day and/or month and/or year missing):

- In case of a partial start date, the therapies are allocated to the phases using the available partial information, no imputation is done. If, for instance, for a therapy start date only month and year is available, these data are compared with the month and year info of the phases.

- In case of a completely missing start date, the therapy is considered as having started before the trial.
- In case of a completely missing end date, the therapy is considered as ongoing at the end of the trial.

3.7. Medical History

Frequency tabulations of medical history will be provided. A listing of medical history will also be provided.

4. EFFICACY

4.1. Level of Significance

No significance testing will be performed in this study. However, a 95% CI will be constructed around the proportion of subjects with SVR and other virologic response parameters.

4.2. Data Handling Rules

Plasma HCV RNA will be determined using an in vitro nucleic acid amplification test for the quantification of HCV RNA in human plasma using a sensitive assay (COBAS® AmpliPrep/COBAS® TaqMan® HCV Test v2.0, lower limit of quantification [LLOQ] = limit of detection [LOD] = 15 IU/mL). HCV RNA determination will be performed at a central laboratory.

Before performing continuous analyses or log transformations, HCV RNA results of '<LLOQ IU/mL HCV RNA DETECTED' will be converted to LLOQ-1 IU/mL and 'HCV RNA NOT DETECTED' will be converted to LOD-2 IU/mL.

Note: We subtract 2 from the LOD to distinguish between '<LLOQ IU/mL HCV RNA DETECTED' and '<HCV RNA NOT DETECTED' in all cases, as the LLOQ could equal the LOD.

For the purpose of sensitivity analysis, missing HCV RNA data for subjects who discontinued early will be imputed using Last Observation Carry Forward(LOCF).

4.3. Efficacy Endpoints

The efficacy endpoints are listed as below:

- The proportion of subjects who have an SVR4, SVR8, SVR12, SVR18 and SVR24;
- The proportion of subjects with viral relapse
- The proportion of subjects with on-treatment failure
- The proportion of subjects with on-treatment virologic response (HCV RNA Not Detected or HCV RNA <LLOQ)
- Time to achieve on-treatment virologic response (HCV RNA Not Detected or HCV RNA <LLOQ)

4.3.1. Definitions

SVRx is defined as follows:

- 1=success:
  - at the time point of SVR
    - HCV RNA Not Detected or
    - HCV RNA <LLOQ and
      - the sample is a confirmation* sample or
      - the sample is the last available HCV RNA measurement or
      - at the next available measurement, HCV RNA Not Detected or HCV RNA <LLOQ Detected
    - ≥ LLOQ quantifiable and
      - the sample is not a confirmatory sample* and
      - not the last available measurement in the study and
      - a next measurement is available and HCV RNA Not Detected or HCV RNA <LLOQ for this next measurement
- 0= failure: otherwise

* Confirmed means that the criterion should be fulfilled at 2 or more consecutive time points or at the last observed time point.

Add 'The LLOQ for the HCV RNA COBAS® AmpliPrep/COBAS® TaqMan® Test v2.0, used in this study, is 15 IU/mL.' as a footnote.

Time point of SVR24 is defined as:

- 24 weeks after the actual EOT (Select the measurement in the SVR24 analysis window. If >1 measurements are present in this window then select the one latest in time.)
- or, if not available, the first available measurement at least 24 weeks after the actual EOT (ie, the first available measurement after the SVR24 analysis window)
- or, if not available, the last measurement available in the SVR18 analysis window, on condition that the time point of SVR24 has been reached
- or, if not available, the last measurement available in the SVR12 analysis window, on condition that the time point of SVR24 has been reached
- or, if not available, the subject is considered to have not achieved SVR24.

Time point of SVR18 is defined as:

- 18 weeks after the actual EOT (Select the measurement in the SVR18 analysis window. If >1 measurements are present in this window then select the one latest in time.)

- or, if not available, the first available measurement at least 18 weeks after the actual EOT (ie, the first available measurement after the SVR18 analysis window)
- or, if not available, the last measurement available in the SVR12 analysis window, on condition that the time point of SVR18 has been reached
- or, if not available, the subject is considered to have not achieved SVR18.

Time point of SVR12 is defined as:

- 12 weeks after the actual EOT (Select the measurement in the SVR12 analysis window. If >1 measurements are present in this window then select the one latest in time.)
- or, if not available, the first available measurement at least 12 weeks after the actual EOT (ie, the first available measurement after the SVR12 analysis window)
- or, if not available (ie, no measurement at least 12 weeks after the actual EOT), the subject is considered a failure.

Time point SVR4 and time point SVR8 are defined similarly as time point SVR12 as above.

Evaluated in the treatment phase:

On-Treatment Virologic Response is defined as follows:

- 0 = HCV RNA result not satisfying a specified threshold
- 1 = HCV RNA result satisfying a specified threshold

The following thresholds will be considered at any time point during treatment:

- HCV RNA Not Detected
- HCV RNA <lower limit of quantification (LLOQ) (detected or not detected)

Note: virologic response will always be calculated as on-treatment response; therefore, the denominator will only include those subjects with valid on-treatment HCV RNA per analysis time point.

Other definitions of virologic response:

vRVR (Very Rapid Virologic Response): HCV RNA Not Detected at Week 2 of treatment (the denominator for the proportion of subjects with vRVR will be the number of subjects who have a nonmissing Week 2 measurement while on therapy (or within 3 days of the date of last dose))

RVR (Rapid Virologic Response): HCV RNA Not Detected at Week 4 of treatment (the denominator for the proportion of subjects with RVR will be the number of subjects who have a nonmissing Week 4 measurement while on therapy (or within 3 days of the date of last dose))

Time to On-treatment Virologic Response is defined as: The number of days since the first day of medication intake until the first day that the threshold (HCV RNA Not Detected or HCV RNA <LLOQ) was achieved.

On-treatment Failure is defined as: Subjects who do not achieve SVR12, with confirmed HCV RNA ≥LLOQ at the actual EOT. Includes subjects with:

- **viral breakthrough**, defined as a confirmed* increase of >1.0 $\log_{10}$ IU/mL in HCV RNA from nadir, or confirmed HCV RNA >2.0 $\log_{10}$ IU/mL in subjects whose HCV RNA had previously been <LLOQ while on treatment.
- other with confirmed HCV RNA ≥LLOQ at the actual EOT (eg, completed study drug treatment, discontinued due to AEs, withdrawal of consent).

*Confirmed means that the criterion should be fulfilled at 2 or more consecutive time points or at the last observed time point.

The proportion of subjects with a viral breakthrough is defined as follows:

- 0 = subject has not had a viral breakthrough (see definition above) up to the considered time point
- 1 = subject has a viral breakthrough at the considered timepoint or has had a viral breakthrough before (regardless of the HCV RNA result at the considered time point)

Evaluated in the treatment and follow-up phases:

Failure: subjects not achieving SVR12 including:

- In the treatment phase: On-treatment failure (see above)
- In the follow-up phase: Posttreatment failure, includes subjects with:
  - Viral relapse after completed treatment
  - Viral relapse after premature discontinuation of treatment
  - Missing HCV RNA at timepoint of SVR12.

Type of failure: if more than 1 type of failure occurs, the order as presented below should be respected:

1. Viral Relapse
2. Viral breakthrough
3. Confirmed HCV RNA ≥LLOQ at EOT
4. Missing at timepoint of SVR12

Evaluated in the follow-up phase:

Viral relapse is defined as follows:

1 = viral relapse

- Subject is not achieving SVR12 (see above)

and

- Subject is not an on-treatment failure (see above)

and

- Post treatment HCV RNA measurement fulfill one of the following conditions:
- at least 2 consecutive measurements are ≥ LLOQ IU/mL quantifiable

or

- the last available measurement is ≥ LLOQ IU/mL quantifiable

0 = no viral relapse: at least one posttreatment measurement available and not a viral relapse

2 = no posttreatment HCV RNA measurements available

Note: viral relapse will only be assessed for those subjects with no on-treatment failure. The denominator will only include those subjects with values 0 and 1.

Late Viral relapse is defined as follows:

1 = late viral relapse

- Subject is achieving SVR12 (see above)

and

- Post treatment HCV RNA measurement beyond the SVR12 time point fulfill one the following conditions:
  - ♦ at least 2 consecutive measurements are ≥ LLOQ IU/mL quantifiable

or

- the last available measurement is ≥ LLOQ IU/mL quantifiable

0 = no late viral relapse: at least one measurement after the time point of SVR12 available and not a late viral relapse.

2 =no measurement after time point of SVR12 available.

Note: late viral relapse will only be assessed for those subjects with no on-treatment failure and no viral relapse. The denominator will only include those subjects with values 0 and 1.

4.3.2. Analysis Methods

All efficacy analyses will be using the full analysis set by cohort.

Descriptive statistics (n, mean (SD), median, interquartile ranges and ranges) per time point by treatment cohort for the continuous parameters (actual values and change from baseline in $\log_{10}$ for HCV RNA). Corresponding listings will be presented. Mean (SD) plots will be produced for actual values and change from baseline in $\log_{10}$ for HCV RNA by treatment cohort.

Tabulations (numbers, proportions and 95% CI) per cohort and time point for SVR4, SVR8, SVR12, SVR18 and SVR24 will be provided. The sensitivity analysis with LOCF applied to missing HCV RNA data will also be performed. The number and proportion of subjects with on-treatment failure and on-treatment virologic response will be tabulated by cohort and overall. Corresponding listings will be presented.

For time to on-treatment virologic response, descriptive statistics (n, mean (SD), median, interquartile ranges and ranges) by treatment cohort will be tabulated.

Subgroup analyses as defined in Section 2.4 will be performed for the selected endpoints.

In addition, the reason for failure will be explored by type of failure (see definition of failure above). If more than one type of failure occurs, the order as presented below should be respected:

1. viral relapse
2. viral breakthrough
3. confirmed HCV RNA ≥LLOQ at the actual EOT
4. missing at time point of SVR12

4.3.3. Treatment Stopping Rules

All study drugs will be discontinued for any subject with viral breakthrough (see the definition in Section 4.3.1). Additionally, an individual subject may stop one or all study drugs if a specific toxicity is met (see Section 6.4 of the protocol for full details).

The occurrence of any one of the following treatment-emergent events in any ongoing study using ODV at therapeutic doses:

- 2nd degree Mobitz Type 2 or 3rd degree heart block;
- drop in EF by ≥10 points with absolute EF <50%;
- a cardiac event that is serious, severe or life-threatening;

will lead to stop of recruitment and dosing in all subjects in the current study if adjudicated by the DRC to be at least possibly related to the study regimen. Such event(s) will be reported to the sponsor medical monitor within 24 hours. Upon this notification, a safety assessment of the event by the DRC will take place within 48 hours and the outcome of the assessment and its associated action towards the study will be reported to Health Authorities and Ethics Committees in compliance with safety reporting regulations, as applicable.

5. VIROLOGY

5.1. Virology Assessments

5.1.1. Viral strain typing

The HCV geno/subtype is determined at screening for study eligibility/stratification using the HCV LiPA v2.0 test and in case no result is obtained the NS5B-based test is used as reflex. In addition, the HCV geno/subtype is determined at baseline for efficacy and virology analyses using the NS5B-based test. In case no result at baseline is obtained, the screening results are used for efficacy and virology analyses.

5.1.2. Viral sequencing

The HCV NS3/4A, NS5A and NS5B regions are sequenced using Next Generation Sequencing (1% read frequency cut-off) in all subjects at baseline and postbaseline in subjects not achieving SVR, focusing on the time of virologic failure and the end of study.

5.2. Virology Definitions

Baseline polymorphisms are defined as amino acid differences from a HCV reference strain with a read frequency ≥15%. The reference strains used for the genotypes included in the study are shown in Table 4.

Table 4: Reference Strain for Genotypes

Genotype	Reference Strain (GenBank Accession ID)
1a	H77 (NC_004102)
1b	Con1 (AJ238799)
Other genotype 1 subtypes or subtype unknown	H77 (NC_004102)
2	JFH-1 (AB047639)

Treatment-emergent substitutions are defined as amino acids detected postbaseline ≥15% and not detected (ie, <1%) at baseline.

Treatment-enriched substitutions are amino acids detected at baseline with a read frequency ≥1% and <15%, and with an increase in read frequency of at least 15% postbaseline.

Return to Baseline is defined as a treatment-emergent substitution which is no longer detected (ie <1%) at end of study, but instead the baseline amino acid is observed.

Resistance-associated substitutions (RASs) are amino acids present at baseline or postbaseline at the positions of interest (see below) in the sequenced regions which are known to confer resistance to one of the drugs. Of note, not all amino acids at the positions of interest are RASs.

HCV NS3 positions of interest:

- List of 18 positions associated with resistance to NS3/4A protease inhibitors: 36, 41, 43, 54, 55, 80, 107, 122, 132, 138, 155, 156, 158, 168, 169, 170, 174 and 175
- List of 8 positions associated with resistance to SMV: 43, 80, 122, 132, 155, 156, 168 and 170

HCV NS5A positions of interest:

- List of 18 positions associated with resistance to NS5A inhibitors: 6, 21, 23, 24, 28, 29, 30, 31, 32, 37, 38, 52, 54, 58, 62, 64, 92, and 93
- List of 8 position associated with resistance to ODV: 28, 29, 30, 31, 32, 58, 92, and 93

HCV NS5B positions of interest:

- List of 9 positions associated with resistance to nucleotide analog NS5B polymerase inhibitors: 96, 142, 159, 223, 226, 282, 316, 320, and 321

Virologic Failure (VF): subjects not achieving SVR12 for virologic reasons, including on-treatment failure, ie, viral breakthrough (VBT) or confirmed HCV RNA ≥LLOQ at end of treatment (EOT) for subjects who completed treatment, and viral relapse.

Non-VF excluded population: FAS population excluding the subjects who did not achieve SVR12 due to reasons other than VF, including subjects with missing data at the SVR12 time point and subjects who discontinued all treatment prematurely (eg AE or withdrawal of consent).

5.3. Virology Time Points and Samples

Baseline: the sample taken at baseline or, if not available, the sample taken at screening is used.

Time of (virologic) failure: the sample taken at virologic failure (ie at VBT, at actual EOT for subjects with confirmed HCV RNA ≥LLOQ at EOT or at relapse) with sequencing data available or, if not available, the first available sample after virologic failure with sequencing data available is used.

End of Study (EOS): the last available sample with sequencing data available in the study is used.

5.4. Virology Analyses

5.4.1. HCV geno/subtype analyses

The number of subjects by HCV geno/subtype for study analyses will be tabulated in frequency outputs (n, %). In addition, a cross-tabulation will compare the HCV geno/subtypes determined at screening (LiPA with NS5B-based reflex) versus baseline (NS5B-based test).

5.4.2. Resistance analyses

5.4.2.1. Baseline

The prevalence of baseline polymorphisms, ie the number of subjects with baseline polymorphism, will be tabulated in frequency outputs (n, %) and the amino acid changes from reference at baseline will be listed for all subjects using a 1% cut-off. In addition, subgroup analyses by the presence of baseline polymorphisms may be tabulated to evaluate the impact on response as needed.

5.4.2.2. Post-Baseline

Time of Failure

For subjects with failure, the incidence of treatment-emergent and treatment-enriched substitutions will be tabulated (if N ≥10) in frequency outputs (n, %) and the amino acid changes from reference will be listed for all subjects with postbaseline sequencing data using a 1% cut-off.

End of Study

The return to baseline at end of study for the subjects with failure and treatment-emergent substitutions at time of failure will be tabulated (if N≥10) in frequency outputs (n, %) as well as the treatment-emergent substitutions at end of study in the subjects who did not return to baseline.

5.4.2.3. Over the Study Period

For the subjects with failure HCV RNA profiles and listings include the reason of failure, relevant baseline disease and demographic characteristics, all amino acid changes from reference at baseline, time of failure and end of study using a 1% cut-off as well as the sequencing follow-up time will be generated. Similar HCV RNA profiles and listings will be generated for subjects with a late viral relapse.

Kaplan-Meier graphs and descriptive statistics will be calculated (if N≥5) to evaluate the time to return to baseline sequence in subjects with failure and treatment-emergent substitutions at time of failure.

6. SAFETY

Unless specified, all safety analysis will use safety analysis set.

6.1. Adverse Events

All reported adverse events (AEs) that are onset during the treatment or follow up phases will be included in the analysis. The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

6.1.1. Definitions

AEs are allocated to the study phases. The phase allocation of AEs consists of a combination of two steps:

- AEs are allocated to phases
- Overlapping/consecutive AEs are combined.

This is detailed in Appendix 1.

Treatment-emergent Adverse Events (TEAEs) are AEs that start on or after the first dose or that are a consequence of a preexisting condition that has worsened since baseline.

AE Duration is calculated as: AE End date – AE Start date + 1.

Prevalence: is defined as the total number of events that occurred (not necessarily new occurrence) in a given time period. The denominator for calculating prevalence and comparable incidence (new occurrences during the same time period) rates will be based on the number of subjects still on treatment at the start of the time period. Note that prevalence counts any AEs regardless whether they are new or sustained from onset prior to the start of the current time interval while comparable incidence refers to new AEs only reported in the current time interval.

Events of Special Interest:

- Cardiac Events
- Increased Bilirubin

Events of Clinical Interest:

- Rash (all type)
- Photosensitivity conditions
- Pruritus

Note: the search terms for events of special/clinical interest related to MedDRA and MedDRA SMQ are listed in Appendix 2.

6.1.2. Analysis Methods

For Adverse Events:

An overall summary will be provided for all adverse events by treatment cohort for each treatment phase separately (Screening phase, treatment phase, follow-up phase and treatment and follow-up phases). Any AEs, serious AEs, AEs with fatal outcome, AEs by WHO toxicity, treatment related AEs, AEs leading to permanent stop of study medication and relation to HCV infection.

The incidence and the incidence rate of treatment-emergent AEs by system organ class (SOC) and preferred term (PT) will be tabulated for each treatment phase separately (Screening phase, treatment phase, follow-up phase and treatment and follow-up phases). TEAEs in at least 10% of subjects will be tabulated separately,

The incidence and incidence rate of AEs with WHO toxicity grade 3 or 4, SAEs, at least possibly treatment related (AL-335, ODV, and SMV) AEs, AE with fatal outcome and AEs leading to permanent stop of study medication will be tabulated by system organ class (SOC) and preferred term (PT).

The incidence and comparable prevalence rate per 2-week time interval for any AEs will be tabulated to evaluate the safety profile over time (treatment and follow-up phase).

Treatment-emergent AEs will be tabulated by SOC and PT for subgroups: Age and BMI (refer to Section 2.4)

A table will be provided for subjects who met study stopping rules, such as 2nd degree Mobitz Type 2 or 3rd degree heart block, cardiac event that is serious, severe or life-threatening. Drop in LVEF for Echocardiographic(ECHO) by ≥10 points with absolute LVEF <50% will be presented too.

Listings will be provided for: all AEs, serious AEs, fatal AEs, AEs leading to permanent stop of AL-335, AEs leading to permanent stop of ODV, AEs leading to permanent stop of SMV andgrade 3-4 AEs. Also AE listing will be provided for the events which meet study stopping rules. AEs which occur in screening will also be included in the listings.

For events of interest:

A summary table will be provided for subject incidence with events of interest in treatment and follow-up phases.

The incidence rates of the events of interest by WHO toxicity grades, treatment relationship, with fatal outcome, as an SAE, leading to permanent stop of study medications will be generated in a summary table using frequency and percentage.

The incidence rates will be summarized by PT for each event of interest, and it will be summarized for AEs with worst toxicity grade of 3 or 4 separately as well.

The incidence and prevalence per 2-week time interval will be summarized.

Subgroup analysis by Age, BMI and Gender (refer to Section 2.4) will be conducted for each event of interest by PT.

6.2. Clinical Laboratory Tests

Clinical lab data are collected at the screening, baseline, week 1, week 2, week 4, week 6 (BNP only), week 8 (cohort 1), week 10 (cohort 2), EOT, follow up week 4, follow up week 8, follow up week 12, follow up week 18, and follow up week 24 time points.

Baseline: Defined as Day 1 measurement, if available. If not available, then the last assessment before the first administration of study drug will be used.

6.2.1. Definitions

World Health Organization (WHO) Toxicity grades:

Grades assigned by the central lab will be used. In case no toxicity grades are defined for a test, the abnormalities (above/below normal range) will be used. The abnormalities 'abnormally low' and 'abnormally high' are considered equally important, ie, if a subject has as well an abnormally low as an abnormally high value post baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%). If, for a specific test, the grading list provides distinct limits for abnormally low (=hypo) values as well as for abnormally high (=hyper) values, this test should be repeated for hyper and hypo limits separately in cross-tabulations and in the ADaM database.

For toxicity grades, no distinction will be made between test results of samples obtained under fasting and under nonfasting conditions: in case limits under fasting and nonfasting conditions differ, the limits of the conditions (fasting/nonfasting) of scheduled visits as planned in the clinical trial protocol (CTP) will always be used, also for samples obtained under a different condition (eg, samples of withdrawal visits).

Treatment-emergent:

An abnormality (toxicity grade or abnormality based on normal ranges) will be considered treatment-emergent if it is worse than the baseline. If the baseline is missing, the abnormality is always considered as treatment-emergent. A shift from 'abnormally low' at baseline to 'abnormally high' post baseline (or vice versa) is also treatment-emergent.

6.2.2. Analysis Methods

All analyses will be performed on the treatment and follow-up phases.

Descriptive statistics for the actual values and changes from baseline per timepoint will be performed for all lab parameters with continues values over time by treatment cohort.

Lab toxicity grade and abnormality will be described by frequency and percentage of subjects using below methods:

- Tabulation of the worst treatment-emergent toxicity grade of laboratory parameters
- Tabulation by worst grade of laboratory parameters where at least one subject had worst treatment emergent WHO toxicity grade >=3 during the Treatment Phase
- Cross-tabulation of the worst toxicity grades versus baseline
- Cross-tabulation of toxicity grades versus baseline over time
- Cross-tabulation of the worst laboratory parameter abnormalities versus baseline

Listing is provided for subjects with toxicity grade 3 or greater. The lab results for subjects who had cardiac events will be listed as well.

All analyses will be done on standardized international (SI)-converted values.

6.3. Vital Signs and Physical Examination Findings

Vital signs are assessed at following time points: Screening, Baseline, Day 2, Weeks1, 2, 3, 4, 6, 8, 10 and 12 (10 & 12 for cohort 2), EOT, FU Week 4, and Week 24.

Baseline: Defined as Day 1 measurement, if available. If not available, then the last assessment before the first administration of study drug will be used.

Assessed vital sign parameters are pulse rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP). All measurements should be taken supine and preceded by at least 5 minutes of rest.

6.3.1. Definitions

Pulse rate, SBP and DBP are classified in the following abnormality codes:

Table 5: Abnormality Codes for Vital Signs

	Pulse (bpm)	DBP (mm Hg)	SBP (mm Hg)
Abnormally low	≤ 50	≤ 50	≤ 90
Grade 1 or mild	-	> 90 - < 100	> 140 - < 160
Grade 2 or moderate	-	≥ 100 - < 110	≥ 160 - < 180
Grade 3 or severe	-	≥ 110	≥ 180
Abnormally high	≥ 120	-	-

In determining the abnormalities, the following rules are applied:

- The worst grades/abnormalities are determined over the whole observational period (over both the treatment and follow-up phases), including postbaseline scheduled and unscheduled measurements
- The abnormalities 'abnormally low' and 'abnormally high'/grades are considered equally important, ie, if a subject has as well an abnormally low as an abnormally high or graded value postbaseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%)

Treatment-emergent:

An abnormality will be considered treatment-emergent if it is worse than the baseline. If the baseline is missing, the abnormality is always considered as treatment-emergent. A shift from 'abnormally low' at baseline to 'abnormally high' or 'grade …' post baseline (or vice versa) is also treatment-emergent.

6.3.2. Analysis Methods

All analyses will be performed on the treatment and follow-up phases. Vital signs data will be analyzed using descriptive statistics on actual values and change from baseline over time by treatment cohort.

Abnormality of vital signs will be described by frequency and percentage using below methods:

- Tabulation of the worst treatment-emergent abnormality of vital signs

- Tabulation of normality/abnormality of vital signs over time
- Cross-tabulations for the worst abnormality versus baseline

Physical examination data will only be listed.

6.4. Electrocardiogram

The electrocardiogram (ECG) variables that will be analyzed are heart rate, PR interval, QRS interval, RR interval, QT interval, and QT interval corrected for heart rate according to Bazett's QT correction (QTcB) and Fridericia's QT correction (QTcF).

ECG data will be collected for the following time points: screening, baseline, day 2, day 3, weeks 1-4, 6, 8, 10 (cohort 2), EOT and follow up week 4. Baseline is the day 1 measurement, if available. If not available, the last assessment before the first administration of study drug will be used.

6.4.1. Definitions

For absolute HR, PR and QRS, the following abnormality categories are defined (Table 6).

Table 6: Abnormality Categories for ECG

	HR	PR	QRS
abnormally low	≤ 50 bpm	< 120 ms	NAP
abnormally high	≥ 120 bpm	> 200 ms	≥ 120 ms

Toxicity grading for PR interval will be performed according to the Division of Aids (DAIDS) grading table for the severity of adult and pediatric adverse events version 1.0, December 2004; clarification August 2009. Please see the Table 7.

Table 7: Toxicity Grading for PR Interval

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life-threatening
Prolonged PR interval				
Adult >16 years	PR interval 0.20 – 0.25 sec*	PR interval >0.25 sec	Type II 2nd degree AV block OR Ventricular pause >3.0 sec	Complete AV block

*Revised by the sponsor.

The toxicity of PR interval will also be coded using the DAIDS grading table (version 2.0, dated 2014) as follows (http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf?sfvrsn=8):

- Grade 1: 210 to <250 msec
- Grade 2: ≥250 msec OR Type I 2nd degree AV block
- Grade 3: Type II 2nd degree AV block OR Ventricular pause ≥3000 msec
- Grade 4: Complete AV block

Analysis for PR will be conducted for all of definitions above (Abnormally high vs low, and toxicity grade per protocol and DAIDS 2.0).

Please note the information for ventricular pause will be provided from medical team.

For absolute QTc parameters the following abnormality categories are defined (based on the ICH E14 Guidance):

- QTc ≤450 msec (normal)
- 450 msec <QTc ≤480 msec (borderline)
- 480 msec <QTc ≤500 msec (prolonged)
- QTc >500 msec (pathologically prolonged).

For increases from baseline in QTc (msec) the following categories are defined (based on ICH E14 Guidance):

- < 30 msec (normal)
- ≥ 30 – 60 msec (borderline)
- > 60 msec (abnormally high)

Only increases in QTc ≥30 msec will be considered as abnormalities.

In determining the abnormalities, the following rules are applied:

- The worst abnormalities are determined over the whole observational period (over both the treatment and Follow up phases), including postbaseline scheduled and unscheduled measurements.
- The abnormalities 'abnormally low' and 'abnormally high' are considered equally important, ie, if a subject has as well an abnormally low as an abnormally high value postbaseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can by more than 100%)

Treatment-emergent:

An abnormality will be considered treatment-emergent if it is worse than the baseline. If the baseline is missing, the abnormality is always considered as treatment-emergent.

6.4.2. Analysis Methods

All analyses will be performed on the treatment and follow-up phases by treatment cohort.

The average of triplicate measurements at each time point will be used for analysis.

Descriptive statistics for the ECG parameters will be calculated for observed values and changes from baseline (CFB) at each scheduled time point.

For individual ECG parameters, the abnormality will be tabulated using frequency and percentage through below methods:

- Tabulation of the worst treatment-emergent ECG abnormalities
- Tabulation of ECG normality/abnormalities over time
- Cross-Tabulation of the Worst ECG Abnormalities in Actual Value versus baseline value
- Cross-Tabulation of the Worst QTc Increase versus the abnormality on the actual value

A listing of ECG abnormalities (all parameters) will be provided. It will contain both actual and CFB values.

6.5. Echocardiography

Echocardiographic (ECHO) data will include Left Ventricular (LV) Ejection Fraction (LVEF) in percent (%). Additional parameters include:

- Systolic Volume (mL)
- Diastolic Volume (mL)
- LV Fractional Shortening (%)
- LV Posterior Wall (PW) Diastolic Thickness (cm)
- Ventricular Septum Diastolic Thickness (cm)

ECHO data will be collected in the following time points: screening, week 4, week 8, EOT, follow up week 4. The last assessment before the first administration of study drug will be used as the baseline.

6.5.1. Definitions

The following definitions are applicable to the ECHO analyses:

- Reversible decrease in LVEF is defined as a decrease of >10% from baseline, which is followed by an increase or a decrease of <=5% from baseline.
- No resolution in LVEF is defined as a decrease of >10% from baseline, which is not followed by an increase or a decrease of <=5% from baseline.

6.5.2. Analysis Methods

All analyses will be performed over the treatment and follow-up phases by treatment cohort.

Descriptive statistics for the ECHO parameters will be calculated for observed values and changes from baseline at each scheduled time point. Number and percent of subjects abnormally low, normal, and abnormally high ECHO parameters by week of study will be summarized for each ECHO parameter.

Number and percentage of subjects with a maximum LVEF change from baseline over all postbaseline visits will be reported for the following categories: decline of >10%, decline of >5 -

≤10%, decline of ≤=5%, increase of >5 - <=10%, increase of >10%, and increase of <5%. Each of the following will also be summarized: The number and percentage of subjects with a maximum decline of baseline over all postbaseline visits of >10% AND:

- Resulting in a LVEF% of <50%.
- A maximum decline of baseline of >10% with reversible decrease.
- A maximum decline of baseline of >10% with no resolution.

And the time to onset for LVEF decrease and duration will also be summarized.

Number and percentage of subjects will be summarized by postbaseline visit for subjects who have a decrease in LVEF of:

- >5% but <=10%
- >10%

A listing of ECHO with actual value, change from baseline, or all parameters will be provided.

6.6. Patient Profiles

A set of patient profiles will be produced for each subject. Data presented will include baseline characteristics, medical history, disposition, study drug exposure, adverse events, HCV RNA levels, lab parameters, ECG parameters, and concomitant medications. Lab parameters will include Bilirubin (all version), AST, ALT, ALP, GGT, Creatine Kinase, Amylase, Lipase, BNP, e-GFR.

7. PHARMACOKINETICS/PHARMACODYNAMICS

Pharmacokinetic (PK) analysis and Pharmacokinetic/Pharmacodynamic analysis will be performed by PK analysis vender and results will be reported by PK analysis vender. Pharmacodynamic (PD) analysis is not planned.

7.1. Pharmacokinetics

Details of the analysis plan and summary of results from Pharmacokinetic analyses will be provided in a separate report by PK analysis vender.

7.2. Immune Response

Not applicable.

7.3. Pharmacodynamics

PD analysis is not planned.

7.4. Pharmacokinetic/Pharmacodynamic Relationships

The Pharmacokinetic/Pharmacodynamic relationship of plasma concentrations and ECG parameters will be evaluated. Details of the analysis plan and summary of results from Pharmacokinetic/Pharmacodynamic analyses will be provided in a separate report.

ATTACHMENTS

APPENDIX 1: PHASE ALLOCATION/COMBINING AES

STEP 1: allocation of events to the phases

Adverse events present in the SDS database are allocated to phases based on their start date. If the start date of an event falls between (or on) the start and stop date of a phase, the AE is attributed to that phase.

Incomplete dates (ie, *day and/or month and/or year missing*)

- Partial start or stop dates:
  1. The partial start date (ie, missing day) will be imputed with the first day of the month unless the month/year is the same as the month/year of an analysis phase. In this situation the incomplete start date will be imputed with the start date of that phase. If the start date of the year is given without specification of the month and date, the partial missing start date will be imputed with the maximum of the first day of the given year and the first date of the first phase.
  2. The partial missing end date (ie, missing day) will be imputed with the last day of the month. If the end date of the year is given without specification of the month and date, the partial missing end date will be imputed with the minimum of the last day of the given year and the end date of the last phase.
- Completely missing start date: the event is allocated to the first active treatment phase (the start date is imputed with the treatment phase start date), except if the end date of the AE falls before the start of the first active treatment phase, in which case it is assigned to the screening phase (the start date is imputed with the screening phase start date).
- Completely missing end date: the following decision rules apply
  1. For completed and discontinued subjects:
     - In case the end date is not flagged as ongoing the date will remain missing.
     - In case the end date is flagged as ongoing the date is imputed by the end date of the last phase.
  2. For ongoing subjects:
     - Missing end dates are imputed by the end date of the last phase (ie, the cut-off date).

STEP 2: combining adverse events

Overlapping/consecutive events are defined as events of the same subject with the same preferred term who have at least 1 day in overlap or for which the start date of an event is 1 day after the end date of the preceding event. Overlapping/consecutive events may be combined into one AE or not, according to the following rules:

1. In case a nonactive phase (eg, Screening) is followed by an active phase, and the overlapping/consecutive events start in both phases, they are allocated to their respective phase and are considered as separate events.
2. In case overlapping/consecutive events start within a single phase, they are considered as one and the same AE. The individual events who contribute to this AE are retained as individual records in the ADAM database but are assigned the same onset, phase, and total duration.
3. In case an active phase is followed by a nonactive phase (eg, Follow-Up), and the overlapping/consecutive events start in both phases, they are allocated to the active phase and are considered as one and the same AE. The individual events who contribute to this AE are retained as individual records in the ADAM database but are assigned the same duration, onset and active phase.
4. In case a nonactive phase is followed by a nonactive phase, and the overlapping/consecutive events start in both phases, they are allocated to their respective phase and are considered as separate AEs.

Events can only be combined into one and the same AE if their start and stop dates are complete. In case the completely missing end date is imputed, this date is also considered as a complete date.

APPENDIX 2A: SEARCH TERMS FOR EVENTS OF SPECIAL/CLINICAL INTEREST

	MedrDRA Term Level	Searching Terms
Events of special interest		
Cardiac Events	SMQ	Please see Appendix 3
Increased Bilirubin	MedDRA PTs	Bilirubin conjugated abnormal Bilirubin conjugated increased Bilirubin excretion disorder Bilirubinuria Blood bilirubin abnormal Blood bilirubin increased Blood bilirubin unconjugated increased Hyperbilirubinaemia Icterus index increased Jaundice Jaundice cholestatic Jaundice extrahepatic obstructive Jaundice hepatocellular Ocular icterus Urine bilirubin increased Yellow skin
Events of clinical interest		
Rash (all type)	MedDRA HLTs, PTs	Erythemas - HLT Papulosquamous conditions - HLT Rashes, eruptions and exanthems NEC - HLT PT: Photodermatosis Photosensitivity reaction Polymorphic light eruption Solar dermatitis Sunburn
	SMQ	SMQ-Severe cutaneous adverse reaction: narrow scope and selected terms of the broad scope(refer Appendix 3)
Pruritus	MedDRA HLT	Pruritus NEC
Photosensitivity conditions	MedDRA PTs	Photodermatosis Photosensitivity reaction Polymorphic light eruption Solar dermatitis Sunburn

APPENDIX 2B: RASH – SMQ19.1

SMQ 19.1: "Severe cutaneous adverse reaction"

SCOPE	Preferred Term
NARROW	CUTANEOUS VASCULITIS
NARROW	DERMATITIS BULLOUS
NARROW	DERMATITIS EXFOLIATIVE
NARROW	DERMATITIS EXFOLIATIVE GENERALISED
NARROW	ERYTHEMA MULTIFORME
NARROW	OCULOMUCOCUTANEOUS SYNDROME
NARROW	SKIN NECROSIS
NARROW	STEVENS-JOHNSON SYNDROME
NARROW	TOXIC EPIDERMAL NECROLYSIS
NARROW	ACUTE GENERALISED EXANTHEMATOUS PUSTULOSIS
NARROW	TOXIC SKIN ERUPTION
NARROW	EPIDERMAL NECROSIS
NARROW	EXFOLIATIVE RASH
NARROW	DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS
BROAD	BLISTER
BROAD	BULLOUS IMPETIGO
BROAD	DRUG ERUPTION
BROAD	EPIDERMOLYSIS BULLOSA
BROAD	MUCOCUTANEOUS ULCERATION
BROAD	NIKOLSKY'S SIGN
BROAD	PEMPHIGOID
BROAD	PEMPHIGUS
BROAD	SKIN EROSION
BROAD	SKIN EXFOLIATION
BROAD	EPIDERMOLYSIS
BROAD	ACQUIRED EPIDERMOLYSIS BULLOSA

APPENDIX 3: CARDIAC EVENTS - SMQ19.1

	Narrow/Broad	PT Term
Cardiac arrhythmias (SMQ)		
Arrhythmia related investigations, signs and symptoms (SMQ)		
	Narrow	Chronotropic incompetence
	Narrow	Electrocardiogram repolarisation abnormality
	Narrow	Electrocardiogram RR interval prolonged
	Narrow	Electrocardiogram U-wave abnormality
	Narrow	Sudden cardiac death
	Broad	Bezold-Jarisch reflex
	Broad	Bradycardia
	Broad	Cardiac arrest
	Broad	Cardiac death
	Broad	Cardiac telemetry abnormal
	Broad	Cardio-respiratory arrest
	Broad	Central bradycardia
	Broad	Electrocardiogram abnormal
	Broad	Electrocardiogram ambulatory abnormal
	Broad	Electrocardiogram change
	Broad	Heart rate abnormal
	Broad	Heart rate decreased
	Broad	Heart rate increased
	Broad	Loss of consciousness
	Broad	Palpitations
	Broad	Rebound tachycardia
	Broad	Sudden death
	Broad	Syncope
	Broad	Tachycardia
	Broad	Tachycardia paroxysmal
Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) (SMQ)		
Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ)		
Bradyarrhythmia terms, nonspecific (SMQ)		
	Narrow	Bradyarrhythmia
	Narrow	Ventricular asystole
Conduction defects (SMQ)		
	Narrow	Accessory cardiac pathway
	Narrow	Adams-Stokes syndrome
	Narrow	Agonal rhythm
	Narrow	Atrial conduction time prolongation
	Narrow	Atrioventricular block
	Narrow	Atrioventricular block complete
	Narrow	Atrioventricular block first degree
	Narrow	Atrioventricular block second degree
	Narrow	Atrioventricular conduction time shortened
	Narrow	Atrioventricular dissociation
	Narrow	Bifascicular block
	Narrow	Brugada syndrome
	Narrow	Bundle branch block
	Narrow	Bundle branch block bilateral
	Narrow	Bundle branch block left
	Narrow	Bundle branch block right
	Narrow	Conduction disorder
	Narrow	Defect conduction intraventricular
	Narrow	Electrocardiogram delta waves abnormal

				Narrow/Broad	PT Term
				Narrow	Electrocardiogram PQ interval prolonged
				Narrow	Electrocardiogram PQ interval shortened
				Narrow	Electrocardiogram PR prolongation
				Narrow	Electrocardiogram PR shortened
				Narrow	Electrocardiogram QRS complex prolonged
				Narrow	Electrocardiogram QT prolonged
				Narrow	Electrocardiogram repolarisation abnormality
				Narrow	Lenegre's disease
				Narrow	Long QT syndrome
				Narrow	Paroxysmal atrioventricular block
				Narrow	Sinoatrial block
				Narrow	Trifascicular block
				Narrow	Ventricular dyssynchrony
				Narrow	Wolff-Parkinson-White syndrome
			Disorders of sinus node function (SMQ)		
				Narrow	Nodal arrhythmia
				Narrow	Nodal rhythm
				Narrow	Sinus arrest
				Narrow	Sinus arrhythmia
				Narrow	Sinus bradycardia
				Narrow	Sinus node dysfunction
				Narrow	Wandering pacemaker
		Cardiac arrhythmia terms, nonspecific (SMQ)			
				Narrow	Arrhythmia
				Narrow	Heart alternation
				Narrow	Heart rate irregular
				Narrow	Pacemaker generated arrhythmia
				Narrow	Pacemaker syndrome
				Narrow	Paroxysmal arrhythmia
				Narrow	Pulseless electrical activity
				Narrow	Reperfusion arrhythmia
				Narrow	Withdrawal arrhythmia
		Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) (SMQ)			
			Supraventricular tachyarrhythmias (SMQ)		
				Narrow	Arrhythmia supraventricular
				Narrow	Atrial fibrillation
				Narrow	Atrial flutter
				Narrow	Atrial parasystole
				Narrow	Atrial tachycardia
				Narrow	Junctional ectopic tachycardia
				Narrow	Sinus tachycardia
				Narrow	Supraventricular extrasystoles
				Narrow	Supraventricular tachyarrhythmia
				Narrow	Supraventricular tachycardia
				Broad	ECG P wave inverted
				Broad	Electrocardiogram P wave abnormal
				Broad	Retrograde p-waves
			Tachyarrhythmia terms, nonspecific (SMQ)		
				Narrow	Anomalous atrioventricular excitation
				Narrow	Cardiac fibrillation
				Narrow	Cardiac flutter
				Narrow	Extrasystoles
				Narrow	Tachyarrhythmia

				Narrow/Broad	PT Term
Ventricular tachyarrhythmias (SMQ)					
				Narrow	Accelerated idioventricular rhythm
				Narrow	Cardiac fibrillation
				Narrow	Parasystole
				Narrow	Rhythm idioventricular
				Narrow	Torsade de pointes
				Narrow	Ventricular arrhythmia
				Narrow	Ventricular extrasystoles
				Narrow	Ventricular fibrillation
				Narrow	Ventricular flutter
				Narrow	Ventricular parasystole
				Narrow	Ventricular pre-excitation
				Narrow	Ventricular tachyarrhythmia
				Narrow	Ventricular tachycardia
Cardiac failure (SMQ)					
				Narrow	Acute left ventricular failure
				Narrow	Acute pulmonary oedema
				Narrow	Acute right ventricular failure
				Narrow	Cardiac asthma
				Narrow	Cardiac failure
				Narrow	Cardiac failure acute
				Narrow	Cardiac failure chronic
				Narrow	Cardiac failure congestive
				Narrow	Cardiac failure high output
				Narrow	Cardiogenic shock
				Narrow	Cardiopulmonary failure
				Narrow	Cardiorenal syndrome
				Narrow	Chronic left ventricular failure
				Narrow	Chronic right ventricular failure
				Narrow	Cor pulmonale
				Narrow	Cor pulmonale acute
				Narrow	Cor pulmonale chronic
				Narrow	Ejection fraction decreased
				Narrow	Hepatic congestion
				Narrow	Hepatojugular reflux
				Narrow	Left ventricular failure
				Narrow	Low cardiac output syndrome
				Narrow	Neonatal cardiac failure
				Narrow	Obstructive shock
				Narrow	Pulmonary oedema
				Narrow	Pulmonary oedema neonatal
				Narrow	Radiation associated cardiac failure
				Narrow	Right ventricular ejection fraction decreased
				Narrow	Right ventricular failure
				Narrow	Ventricular failure
				Broad	Artificial heart implant
				Broad	Atrial natriuretic peptide abnormal
				Broad	Atrial natriuretic peptide increased
				Broad	Bendopnoea
				Broad	Brain natriuretic peptide abnormal
				Broad	Brain natriuretic peptide increased
				Broad	Cardiac cirrhosis
				Broad	Cardiac contractility modulation therapy
				Broad	Cardiac index decreased

				Narrow/Broad	PT Term
				Broad	Cardiac output decreased
				Broad	Cardiac resynchronisation therapy
				Broad	Cardiac ventriculogram abnormal
				Broad	Cardiac ventriculogram left abnormal
				Broad	Cardiac ventriculogram right abnormal
				Broad	Cardiomegaly
				Broad	Cardio-respiratory distress
				Broad	Cardiothoracic ratio increased
				Broad	Central venous pressure increased
				Broad	Diastolic dysfunction
				Broad	Dilatation ventricular
				Broad	Dyspnoea paroxysmal nocturnal
				Broad	Heart transplant
				Broad	Hepatic vein dilatation
				Broad	Jugular vein distension
				Broad	Left ventricular dilatation
				Broad	Left ventricular dysfunction
				Broad	Left ventricular enlargement
				Broad	Lower respiratory tract congestion
				Broad	Myocardial depression
				Broad	Nocturnal dyspnoea
				Broad	N-terminal prohormone brain natriuretic peptide abnormal
				Broad	N-terminal prohormone brain natriuretic peptide increased
				Broad	Oedema
				Broad	Oedema due to cardiac disease
				Broad	Oedema neonatal
				Broad	Oedema peripheral
				Broad	Orthopnoea
				Broad	Peripheral oedema neonatal
				Broad	Peripheral swelling
				Broad	Post cardiac arrest syndrome
				Broad	Prohormone brain natriuretic peptide abnormal
				Broad	Prohormone brain natriuretic peptide increased
				Broad	Pulmonary congestion
				Broad	Right ventricular dilatation
				Broad	Right ventricular dysfunction
				Broad	Right ventricular enlargement
				Broad	Scan myocardial perfusion abnormal
				Broad	Stroke volume decreased
				Broad	Surgical ventricular restoration
				Broad	Systolic dysfunction
				Broad	Venous pressure increased
				Broad	Venous pressure jugular abnormal
				Broad	Venous pressure jugular increased
				Broad	Ventricular assist device insertion
				Broad	Ventricular dysfunction
				Broad	Ventricular dyssynchrony
Cardiomyopathy (SMQ)					
				Narrow	Atrial septal defect acquired
				Narrow	Biopsy heart abnormal
				Narrow	Cardiac amyloidosis
				Narrow	Cardiac hypertrophy

				Narrow/Broad	PT Term
				Narrow	Cardiac sarcoidosis
				Narrow	Cardiac septal hypertrophy
				Narrow	Cardiac siderosis
				Narrow	Cardiomyopathy
				Narrow	Cardiomyopathy acute
				Narrow	Cardiomyopathy alcoholic
				Narrow	Cardiomyopathy neonatal
				Narrow	Cardiotoxicity
				Narrow	Congestive cardiomyopathy
				Narrow	Cytotoxic cardiomyopathy
				Narrow	Diabetic cardiomyopathy
				Narrow	Ejection fraction abnormal
				Narrow	Ejection fraction decreased
				Narrow	Eosinophilic myocarditis
				Narrow	HIV cardiomyopathy
				Narrow	Hypertensive cardiomyopathy
				Narrow	Hypertrophic cardiomyopathy
				Narrow	Ischaemic cardiomyopathy
				Narrow	Metabolic cardiomyopathy
				Narrow	Myocardial calcification
				Narrow	Myocardial fibrosis
				Narrow	Myocardial haemorrhage
				Narrow	Non-obstructive cardiomyopathy
				Narrow	Peripartum cardiomyopathy
				Narrow	Pulmonary arterial wedge pressure increased
				Narrow	Restrictive cardiomyopathy
				Narrow	Right ventricular ejection fraction decreased
				Narrow	Stress cardiomyopathy
				Narrow	Tachycardia induced cardiomyopathy
				Narrow	Thyrotoxic cardiomyopathy
				Narrow	Ventricular septal defect acquired
				Narrow	Viral cardiomyopathy
				Broad	Abnormal precordial movement
				Broad	Acquired cardiac septal defect
				Broad	Acute left ventricular failure
				Broad	Alcohol septal ablation
				Broad	Allergic myocarditis
				Broad	Arrhythmia
				Broad	Arrhythmia supraventricular
				Broad	Artificial heart implant
				Broad	Ascites
				Broad	Atrial hypertrophy
				Broad	Atrial pressure increased
				Broad	Autoimmune myocarditis
				Broad	Bendopnoea
				Broad	Blood pressure diastolic abnormal
				Broad	Blood pressure diastolic decreased
				Broad	Blood pressure diastolic increased
				Broad	Blood pressure fluctuation
				Broad	Blood pressure inadequately controlled
				Broad	Blood pressure systolic abnormal
				Broad	Blood pressure systolic decreased
				Broad	Blood pressure systolic increased
				Broad	Cardiac aneurysm

				Narrow/Broad	PT Term
				Broad	Cardiac arrest
				Broad	Cardiac contractility modulation therapy
				Broad	Cardiac electrophysiologic study abnormal
				Broad	Cardiac failure
				Broad	Cardiac failure acute
				Broad	Cardiac failure chronic
				Broad	Cardiac failure congestive
				Broad	Cardiac function test abnormal
				Broad	Cardiac imaging procedure abnormal
				Broad	Cardiac index abnormal
				Broad	Cardiac index decreased
				Broad	Cardiac index increased
				Broad	Cardiac monitoring abnormal
				Broad	Cardiac operation
				Broad	Cardiac output decreased
				Broad	Cardiac pseudoaneurysm
				Broad	Cardiac resynchronisation therapy
				Broad	Cardiac ventricular scarring
				Broad	Cardiac ventriculogram abnormal
				Broad	Cardiac ventriculogram left abnormal
				Broad	Cardiac ventriculogram right abnormal
				Broad	Cardiomegaly
				Broad	Cardiothoracic ratio increased
				Broad	Cardiovascular disorder
				Broad	Cardiovascular function test abnormal
				Broad	Chest pain
				Broad	Chest X-ray abnormal
				Broad	Computerised tomogram thorax abnormal
				Broad	Coxsackie carditis
				Broad	Coxsackie myocarditis
				Broad	Cytomegalovirus myocarditis
				Broad	Decreased ventricular preload
				Broad	Diastolic dysfunction
				Broad	Dilatation atrial
				Broad	Dilatation ventricular
				Broad	Directional Doppler flow tests abnormal
				Broad	Dyspnoea
				Broad	ECG signs of ventricular hypertrophy
				Broad	Echocardiogram abnormal
				Broad	Electrocardiogram abnormal
				Broad	Electrocardiogram change
				Broad	Endocardial fibroelastosis
				Broad	External counterpulsation
				Broad	Gonococcal heart disease
				Broad	Heart and lung transplant
				Broad	Heart transplant
				Broad	Hepatomegaly
				Broad	Hyperdynamic left ventricle
				Broad	Increased ventricular preload
				Broad	Irregular breathing
				Broad	Labile blood pressure
				Broad	Left atrial dilatation
				Broad	Left atrial enlargement
				Broad	Left ventricular dilatation

				Narrow/Broad	PT Term
				Broad	Left ventricular end-diastolic pressure decreased
				Broad	Left ventricular enlargement
				Broad	Left ventricular failure
				Broad	Left ventricular heave
				Broad	Lupus myocarditis
				Broad	Lyme carditis
				Broad	Malarial myocarditis
				Broad	Mental status changes
				Broad	Multiple gated acquisition scan abnormal
				Broad	Myocardiac abscess
				Broad	Myocardial necrosis marker increased
				Broad	Myocarditis
				Broad	Myocarditis bacterial
				Broad	Myocarditis helminthic
				Broad	Myocarditis infectious
				Broad	Myocarditis meningococcal
				Broad	Myocarditis mycotic
				Broad	Myocarditis post infection
				Broad	Myocarditis septic
				Broad	Myocarditis syphilitic
				Broad	Myocarditis toxoplasmal
				Broad	Myoglobinaemia
				Broad	Myoglobinuria
				Broad	Nocturia
				Broad	Nuclear magnetic resonance imaging thoracic abnormal
				Broad	Oedema
				Broad	Orthostatic hypotension
				Broad	Palpitations
				Broad	Papillary muscle disorder
				Broad	Papillary muscle haemorrhage
				Broad	Radiation myocarditis
				Broad	Right atrial dilatation
				Broad	Right atrial enlargement
				Broad	Right atrial pressure increased
				Broad	Right ventricle outflow tract obstruction
				Broad	Right ventricular dilatation
				Broad	Right ventricular enlargement
				Broad	Right ventricular heave
				Broad	Right ventricular systolic pressure decreased
				Broad	Scan myocardial perfusion abnormal
				Broad	Sudden cardiac death
				Broad	Sudden death
				Broad	Surgical ventricular restoration
				Broad	Syncope
				Broad	Systolic anterior motion of mitral valve
				Broad	Systolic dysfunction
				Broad	Ultrasound Doppler abnormal
				Broad	Vascular resistance pulmonary increased
				Broad	Ventricular arrhythmia
				Broad	Ventricular assist device insertion
				Broad	Ventricular dysfunction
				Broad	Ventricular dyskinesia
				Broad	Ventricular dyssynchrony

				Narrow/Broad	PT Term
				Broad	Ventricular hyperkinesia
				Broad	Ventricular hypertrophy
				Broad	Ventricular hypokinesia
				Broad	Ventricular remodelling
				Broad	Viral myocarditis
Ischaemic heart disease (SMQ)					
	Myocardial infarction (SMQ)				
				Narrow	Acute coronary syndrome
				Narrow	Acute myocardial infarction
				Narrow	Angina unstable
				Narrow	Blood creatine phosphokinase MB abnormal
				Narrow	Blood creatine phosphokinase MB increased
				Narrow	Coronary artery embolism
				Narrow	Coronary artery occlusion
				Narrow	Coronary artery reocclusion
				Narrow	Coronary artery thrombosis
				Narrow	Coronary bypass thrombosis
				Narrow	Coronary vascular graft occlusion
				Narrow	Kounis syndrome
				Narrow	Myocardial infarction
				Narrow	Myocardial necrosis
				Narrow	Myocardial reperfusion injury
				Narrow	Myocardial stunning
				Narrow	Papillary muscle infarction
				Narrow	Post procedural myocardial infarction
				Narrow	Postinfarction angina
				Narrow	Silent myocardial infarction
				Narrow	Troponin I increased
				Narrow	Troponin increased
				Narrow	Troponin T increased
				Broad	Blood creatine phosphokinase abnormal
				Broad	Blood creatine phosphokinase increased
				Broad	Cardiac ventricular scarring
				Broad	ECG electrically inactive area
				Broad	ECG signs of myocardial infarction
				Broad	Electrocardiogram Q wave abnormal
				Broad	Electrocardiogram ST segment abnormal
				Broad	Electrocardiogram ST segment elevation
				Broad	Electrocardiogram ST-T segment elevation
				Broad	Infarction
				Broad	Myocardial necrosis marker increased
				Broad	Scan myocardial perfusion abnormal
				Broad	Vascular graft occlusion
				Broad	Vascular stent occlusion
				Broad	Vascular stent thrombosis
Shock (SMQ)					
	Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (SMQ)				
				Narrow	Acute left ventricular failure
				Narrow	Adams-Stokes syndrome
				Narrow	Atrial parasystole
				Narrow	Cardiac arrest
				Narrow	Cardiac arrest neonatal
				Narrow	Cardiac death
				Narrow	Cardiac fibrillation

				Narrow/Broad	PT Term
				Narrow	Cardiac flutter
				Narrow	Cardiogenic shock
				Narrow	Cardio-respiratory arrest
				Narrow	Cardio-respiratory arrest neonatal
				Narrow	Cardiovascular insufficiency
				Narrow	Circulatory collapse
				Narrow	Obstructive shock
				Narrow	Pulse absent
				Narrow	Pulseless electrical activity
				Narrow	Shock
				Narrow	Shock symptom
				Narrow	Sudden cardiac death
				Narrow	Ventricular asystole
				Narrow	Ventricular fibrillation
				Narrow	Ventricular flutter
				Narrow	Ventricular parasystole
				Broad	Acute kidney injury
				Broad	Acute prerenal failure
				Broad	Acute respiratory failure
				Broad	Anuria
				Broad	Blood pressure immeasurable
				Broad	Cerebral hypoperfusion
				Broad	Grey syndrome neonatal
				Broad	Hepatic congestion
				Broad	Hepatojugular reflux
				Broad	Hepatorenal failure
				Broad	Hypoperfusion
				Broad	Jugular vein distension
				Broad	Myocardial depression
				Broad	Neonatal anuria
				Broad	Neonatal multi-organ failure
				Broad	Neonatal respiratory failure
				Broad	Organ failure
				Broad	Prerenal failure
				Broad	Propofol infusion syndrome
				Broad	Renal failure
				Broad	Renal failure neonatal
				Broad	Respiratory failure
Torsade de pointes/QT prolongation (SMQ)					
				Narrow	Electrocardiogram QT interval abnormal
				Narrow	Electrocardiogram QT prolonged
				Narrow	Long QT syndrome
				Narrow	Long QT syndrome congenital
				Narrow	Torsade de pointes
				Narrow	Ventricular tachycardia
				Broad	Cardiac arrest
				Broad	Cardiac death
				Broad	Cardiac fibrillation
				Broad	Cardio-respiratory arrest
				Broad	Electrocardiogram repolarisation abnormality
				Broad	Electrocardiogram U-wave abnormality
				Broad	Loss of consciousness
				Broad	Sudden cardiac death
				Broad	Sudden death

				Narrow/Broad	PT Term
				Broad	Syncope
				Broad	Ventricular arrhythmia
				Broad	Ventricular fibrillation
				Broad	Ventricular flutter
				Broad	Ventricular tachyarrhythmia