STATISTICAL ANALYSIS PLAN
FOR BMS-790052

A PHASE 3 EVALUATION OF DACLATASVIR AND SOFOSBUVIR WITH RIBAVIRIN IN CIRRHOTIC SUBJECTS WITH GENOTYPE 3 CHRONIC HEPATITIS C INFECTION

PROTOCOL AI444379

VERSION # 1.0

TABLE OF CONTENTS

LIST OF TABLES

Approved v1.0   930118421 1.0

LIST OF FIGURES

1   BACKGROUND AND RATIONALE

Research Hypothesis:

Combination therapy with DCV and SOF plus RBV for 24 weeks is safe and demonstrates an SVR12 rate greater than the threshold SVR rate in chronically infected subjects with HCV GT-3 and cirrhosis.

Schedule of Analyses:

- The analysis for the primary endpoint will be performed after all subjects have reached post-treatment Week 12 (SVR12) ;
- The final analysis (SVR24) will be performed at study completion.

2   STUDY DESCRIPTION

2.1   Study Design

Study design schematic is presented in Figure 2.1-1.

Figure 2.1-1:   **Study Design Schematic**
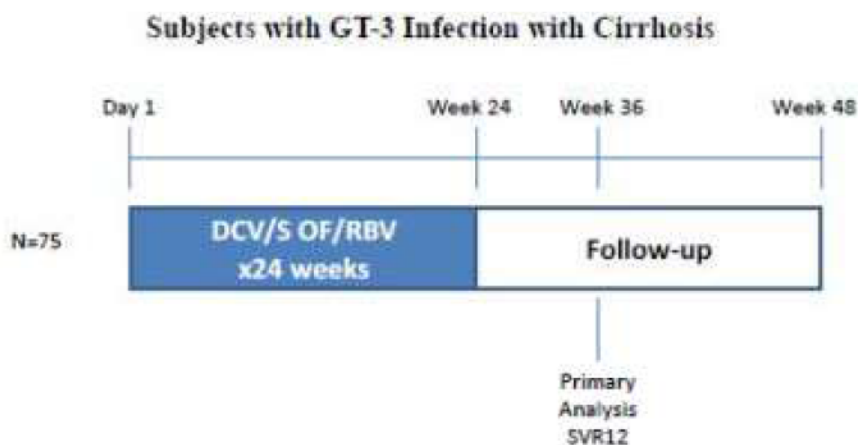
AI444379 is an open label, one-arm trial evaluating the combination therapy of DCV and SOF plus RBV for 24 weeks duration in GT-3 subjects with cirrhosis.

Subjects will receive the combination of DCV 60 mg QD (unless concomitant HIV regimen dictates otherwise) + SOF 400 mg QD + RBV (weight based 1000 mg-1200 mg daily) for 24 weeks.

As an open label study, HCV RNA will be available for review by the clinical site personnel. Any subject who discontinues therapy before the protocol-defined treatment duration should have 24 weeks of post-treatment follow-up. The screening/enrollment period is anticipated to be approximately 8 weeks from FPFV to LPFV. Study duration will be 52 weeks (4 week screening period, 24 weeks of therapy, and 24 weeks of follow-up).

Any subject who receives anti-HCV therapy in the post-treatment period prior to Week 4 (i.e., a subject who discontinued therapy due to an AE or virologic failure who then chooses to receive an alternative therapy outside of the study), should discontinue from the study after completing the post-treatment Week 4 safety visit. If the subject receives HCV therapy after post treatment Week 4, the subject should be discontinued from the study as soon as possible, following completion of the procedures outlined in the Post-treatment Week 24 visit.

The end of the study is defined as the date of the last visit for the last subject to complete the study. The last visit is defined as the last post-treatment follow up subject visit.

2.2   Treatment Assignment

2.3   Blinding and Unblinding

This is an open label study.

2.4   Protocol Amendments

N/A.

3   OBJECTIVES

3.1   Primary

- To demonstrate the SVR12 rate, defined as HCV RNA < LLOQ target detected (TD) or target not detected (TND) at follow-up Week 12 in subjects treated with 24 weeks of DCV+SOF+RBV therapy is greater than the historical threshold SVR rate.

3.2   Key Secondary

- To assess the impact of baseline NS5A resistance-associated polymorphisms on the SVR12 rate.

3.3 Secondary

- To assess safety, as measured by the frequency of deaths, serious adverse events (SAE)s, discontinuation due to adverse events (AE)s, Grade 3/4 AEs and Grade 3/4 lab abnormalities observed from clinical laboratory testing.

- To assess antiviral activity, as measured by

  − The proportion of subjects who achieve HCV RNA < LLOQ-TD or TND at each of the following Weeks: 1, 2, 4, 8, 12, 16, 20, 24, and EOT; post-treatment Weeks 4 and 24.

  − The proportion of subjects who achieve HCV RNA <LLOQ TND at each of the following Weeks: 1, 2, 4, 8, 12, 16, 20, 24, and EOT.

3.4 Exploratory

4 ENDPOINTS

Efficacy analyses will evaluate HCV RNA as measured by the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test [lower limit of quantification (LLOQ): 15 IU/mL].

4.1 Primary Endpoints

Proportion of subjects with SVR12, defined as HCV RNA < LLOQ, target detected (TD) or target not detected (TND) at follow-up Week 12 in all treated subjects. Missing HCV RNA data at follow-up Week 12 will be imputed using the Next Value Carried Backwards (NVCB) approach, i.e., missing HCV RNA data in the follow-up Week 12 window will be imputed using the next and closest available HCV RNA measurement after the follow-up Week 12 HCV RNA window.

4.2 Key Secondary Endpoints

The proportion of subjects who achieve SVR12 in the presence and absence of baseline NS5A resistance-associated polymorphisms.

4.3 Secondary Endpoints

- On treatment safety, as measured by frequency of deaths, SAEs, discontinuations due to AEs, Grade 3/4 AEs, and Grade 3/4 laboratory abnormalities through the end of treatment plus 7 days;

- The proportion of subjects who achieve HCV RNA < LLOQ, TD or TND at each of the following Weeks: 1, 2, 4, 8, 12, 16, 20, 24, and EOT; post-treatment Weeks 4 and 24;

- The proportion of subjects who achieve HCV RNA < LLOQ, TND at each of the following Weeks: 1, 2, 4, 8, 12, 16, 20, 24, and EOT.

4.4   Exploratory Endpoints

███
███
███
███
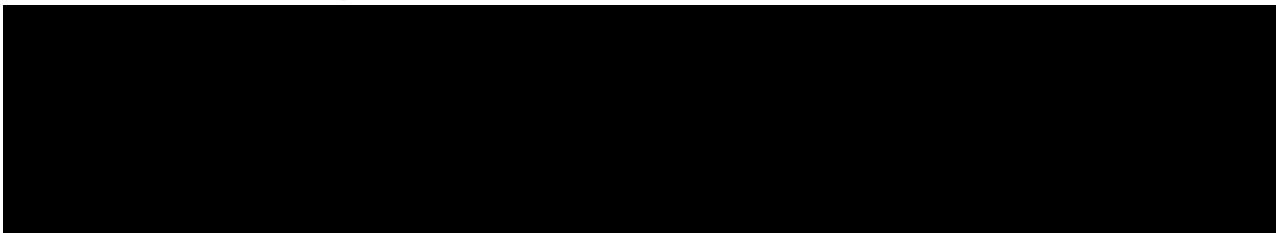
5   SAMPLE SIZE AND POWER

███
███
███
███
███
███
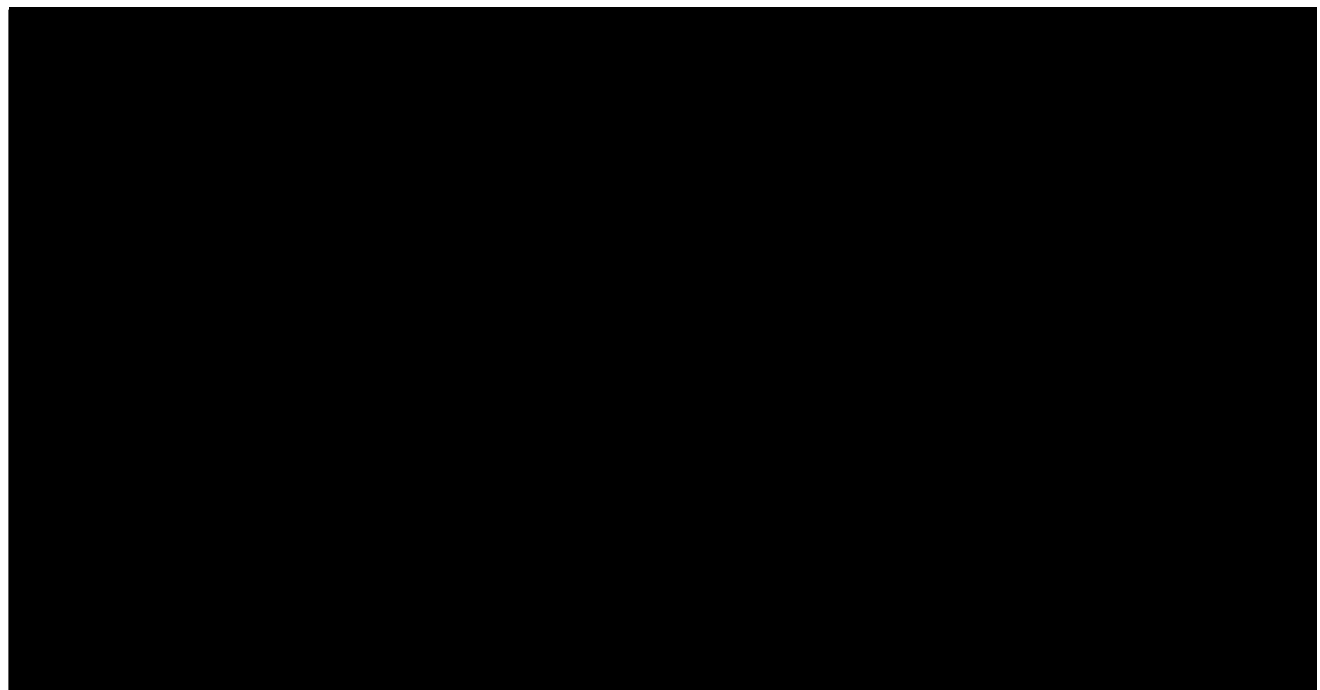
Table 5.1-1 presents some scenarios of observed SVR12 rates and exact binomial 95% confidence intervals.

Table 5.1-1:   SVR12 Observed Rates and Exact Binomial 95% Confidence Intervals (n = 75)

Observed SVR12 Rate	Observed Responders	95% CI
71%	53 of 75	(59.0%, 80.6%)
76%	57 of 75	(64.7%, 85.1%)
80%	60 of 75	(69.2%, 88.4%)
85%	64 of 75	(75.3%, 92.4%)
91%	68 of 75	(81.7%, 96.2%)
96%	72 of 75	(88.8%, 99.2%)

6   STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1   Study Periods

Refer to core Statistical Analysis Plan (Core SAP) Section 6.1.

6.2   Treatment Regimens

All subjects are given the same treatment regimen, DCV+ SOF with RBV through Week 24.

6.3   Populations for Analyses

This is a non-randomized study. Populations for analyses include the following: Enrolled Subjects, Treated Subjects, and Follow-up Subjects. Refer to core SAP Section 6.3 for description of Population for Analyses.

7   STATISTICAL ANALYSES

Statistical analyses are performed using the version of UNIX SAS or S-Plus in production, unless otherwise specified.

7.1   General Methods

Laboratory abnormalities are determined from laboratory measurements analyzed at the central or local laboratory.

Otherwise, refer to Core SAP Section 7.1.

There is only one treatment regimen in this study. Analyses are planned to be presented for all treated subjects by prior HCV therapy status (naive, experienced), coinfection status (HCV monoinfected, HCV/HIV coinfected) and overall. Depending on enrollment, if only a minimum number of HCV/HIV coinfected subjects are enrolled, Analyses will be presented by prior HCV therapy status (naive, experienced) and overall.

7.2   Study Conduct

Refer to Core SAP Section 7.2.

Appendix 1 describes the relevant protocol deviations of this study that can be programmed from the database.

7.3   Study Population

7.3.1   Disposition of Subjects

Refer to Core SAP Section 7.3.

7.3.2   Demographics and Other Baseline Characteristics

7.3.2.1   Demographics

Refer to Core SAP Section 7.3.2.1.

7.3.2.2   Baseline Disease Characteristics and Prognostic Factors

All subjects in this study are GT-3 Infected with cirrhosis.

Otherwise, refer to Core SAP Section 7.3.2.2.

7.3.2.3   Other Baseline Characteristics

Refer to Core SAP Section 7.3.2.3.

7.4   Extent of Exposure

Study therapy of this study is DCV+SOF+RBV.

Refer to Core SAP Section 7.4. In addition, proportions of subjects with RBV dose reduction, and RBV discontinuation will be presented separately. RBV discontinuation will be defined as last RBV dosing date < last treatment dosing date -1. Time to the first RBV dose reduction and time to RBV discontinuation will also be summarized.

Subjects with full RBV dosing, dose reduction or interruptions > 14 days are summarized. A subject listing is generated for all subjects who received a full RBV dose or experienced a reduction or interruption in RBV dose. This listing will include time on study therapy, treatment start and stop dates, weight, target daily dose, total daily dose received, reason for modification, duration adherence, and dose adherence.

7.5   Efficacy

For binary efficacy endpoints, 2-sided 95% CIs will be calculated based on exact binomial distribution.

7.5.1   Primary Efficacy Endpoint

The primary analysis will be performed after all subjects have reached post-treatment Week 12 (SVR12). A final analysis (SVR24) will be performed at study completion.

The primary analysis for the primary endpoint SVR12 will be computed on all treated subjects, and missing HCV RNA data at follow-up Week 12 will be imputed using the Next Value Carried Backwards (NVCB) approach, ie, missing HCV RNA data in the follow-up Week 12 window

will be imputed using the next and closest available HCV RNA measurement after the follow-up Week 12 HCV RNA visit window.

The lower bound of the SVR12 95% confidence interval (CI) will be used to compare to the historical threshold of 79%. If it exceeds 79%, it can be concluded that the primary objective is achieved.

The following sensitivity analyses on the primary endpoint will also be conducted:

- Sensitivity analysis using mITT (Missing=Non-Responder): SVR12 rates and two-sided 95% CIs will use all treated subjects. The SVR12 status for subjects with missing follow-up Week 12 HCV RNA will be counted as non-responders.

- Sensitivity analysis using observed values: SVR12 rates and two-sided 95% CIs will be computed on subjects with observed HCV RNA values. The numerator is based on subject meeting the response criteria. However, the denominator is based on treated subjects with observed HCV RNA at post-treatment Week 12.

7.5.2   Secondary and Other Efficacy Endpoints

7.5.2.1   HCV RNA < LLOQ TD or TND Over Time

The proportion of subjects who achieve HCV RNA < LLOQ TD or TND are presented at each of the following Weeks: 1, 2, 4, 8, 12, 16, 20, 24, and EOT; post-treatment Weeks 4, 12 and 24. Otherwise, refer to Core SAP Section 7.5.2.1.

7.5.2.2   HCV RNA < LLOQ TND Over Time

The proportion of subjects who achieve HCV RNA < LLOQ TND at each of the following Weeks are presented: 1, 2, 4, 8, 12, 16, 20, 24, and EOT; post-treatment Weeks 4, 12 and 24. Otherwise, refer to Core SAP Section 7.5.2.2.
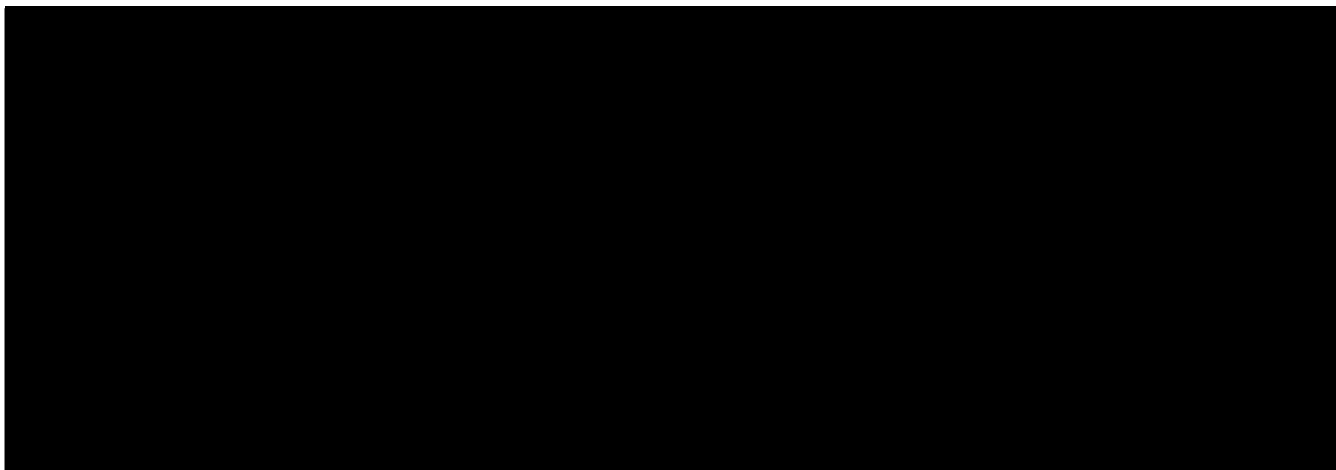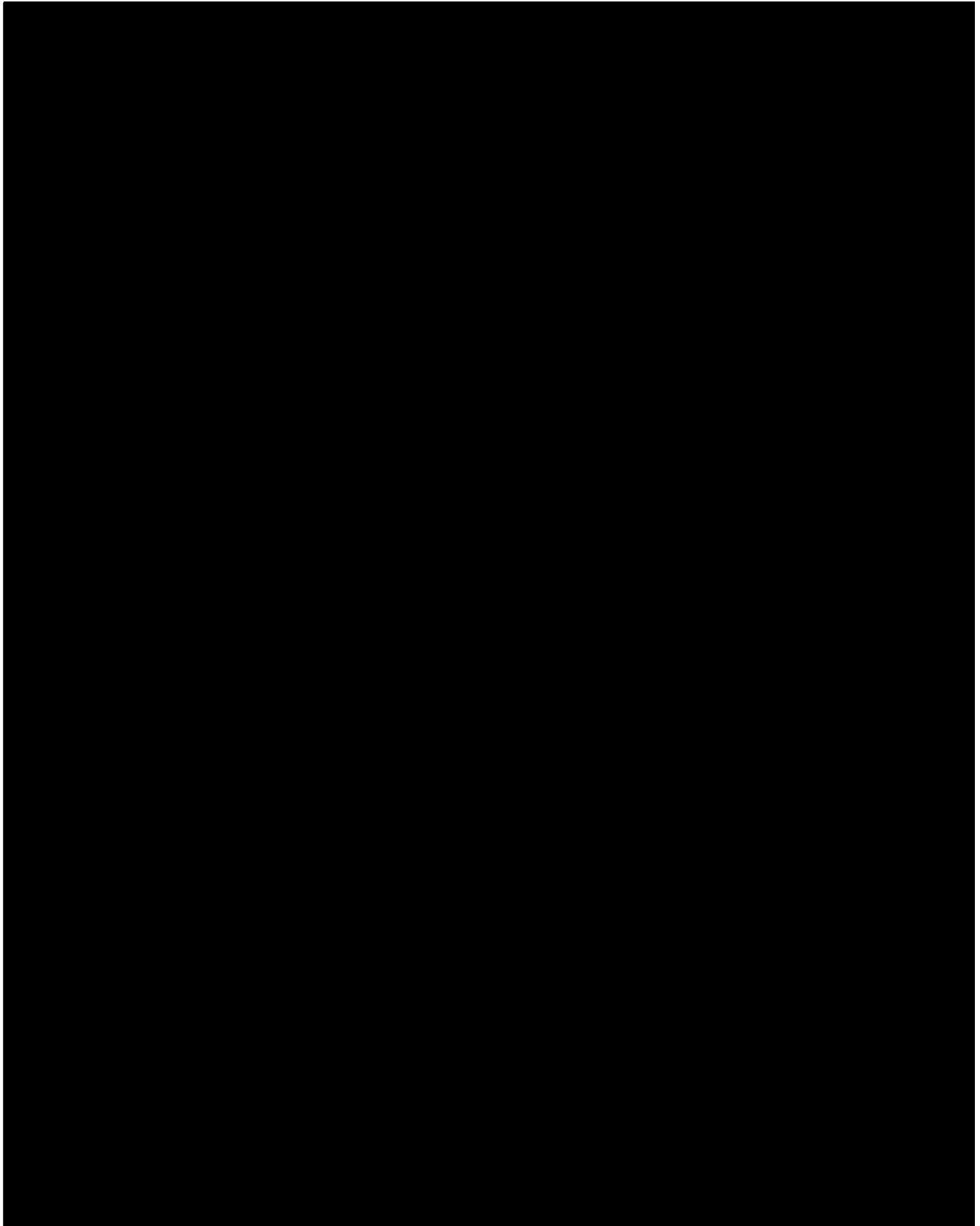
7.5.2.3   HCV RNA Changes from Baseline

Refer to Core SAP Section 7.5.2.3.

7.5.2.4   Concordance between SVR12 and SVR24

Refer to Core SAP Section 7.5.2.4.

7.5.2.5   Efficacy Results in Subgroups

7.6   Safety

Safety endpoints are assessed for all treated subjects, unless otherwise specified. Refer to Core SAP Section 7.6, which includes Sections 7.6.1 to 7.6.11

7.7   Pharmacokinetic Analyses

The Pharmacokinetic (PK) samples collected from the current study may be pooled to perform an integrated population PK analysis, the results of which may be reported separately. All available individual plasma concentrations from all subjects will be listed by nominal time.

7.7.1   *Trough Concentrations*

Pre-dose PK trough samples are collected at weeks 1, 2, 4, 8, 12 and 24 from all treated subjects.

Analyses are based on evaluable PK trough concentrations. The trough concentrations of DCV and possibly SOF and its metabolites (pending the assay availability) from evaluable PK trough samples will be summarized based on nominal time by visit week using (n, mean, SD, geometric mean, CV, median, quartiles, minimum, and maximum). Concentrations less than LLOQ are imputed as LLOQ/2. A listing of all concentration data versus actual time and nominal time will be provided.

A longitudinal plot displays geometric mean of trough concentration versus week.

8   CONVENTIONS

8.1   Visit Definition

Visits are defined below. Subjects receive up to 24 weeks of study therapy and are followed for an additional 24 weeks. Windows are constructed for each visit in order to slot data. Labels for study periods and visits appear in listings and datasets.

Table 8.1-1:   **Visit Definition**

| Study Period Label		Visit Label	Visit Number	Target Day from Start of Study Period	Visit Window
PRE-TREAT		PRE-TREAT	1	1	< 1 day[a]
ON-TREAT		DAY 1	2	1	1 - 4 days
		WEEK 1	3	7	5 days - 11 days
		WEEK 2	4	14	12 days - 3 weeks
		WEEK 4	5	28	> 3 weeks - 6 weeks
		WEEK 8	6	56	> 6 - 10 weeks
		WEEK 12	7	84	> 10 - 14 weeks
		WEEK 16	8	112	> 14 - 18 weeks
		WEEK 20	9	140	> 18 - 22 weeks
		WEEK 24	10	168	> 22 weeks
FOLLOW-UP		F/U WEEK 4	11	21	> 1 - 8 weeks

Table 8.1-1:   **Visit Definition**

Study Period Label		Visit Label	Visit Number	Target Day from Start of Study Period	Visit Window
		F/U WEEK 12	12	77	> 8 - 18 weeks
		F/U WEEK 24	13	161	> 18 weeks

[a] See Section 6.1, Study Periods, for classification of measurements on Day 1 (first dose of active study therapy) as pre-treatment or on-treatment depending on the data domain.

For the definitions of time measurement, windows around planned measurement times, and study day/week, refer to the Core SAP Section 8.1.

8.2   Domain Derivations
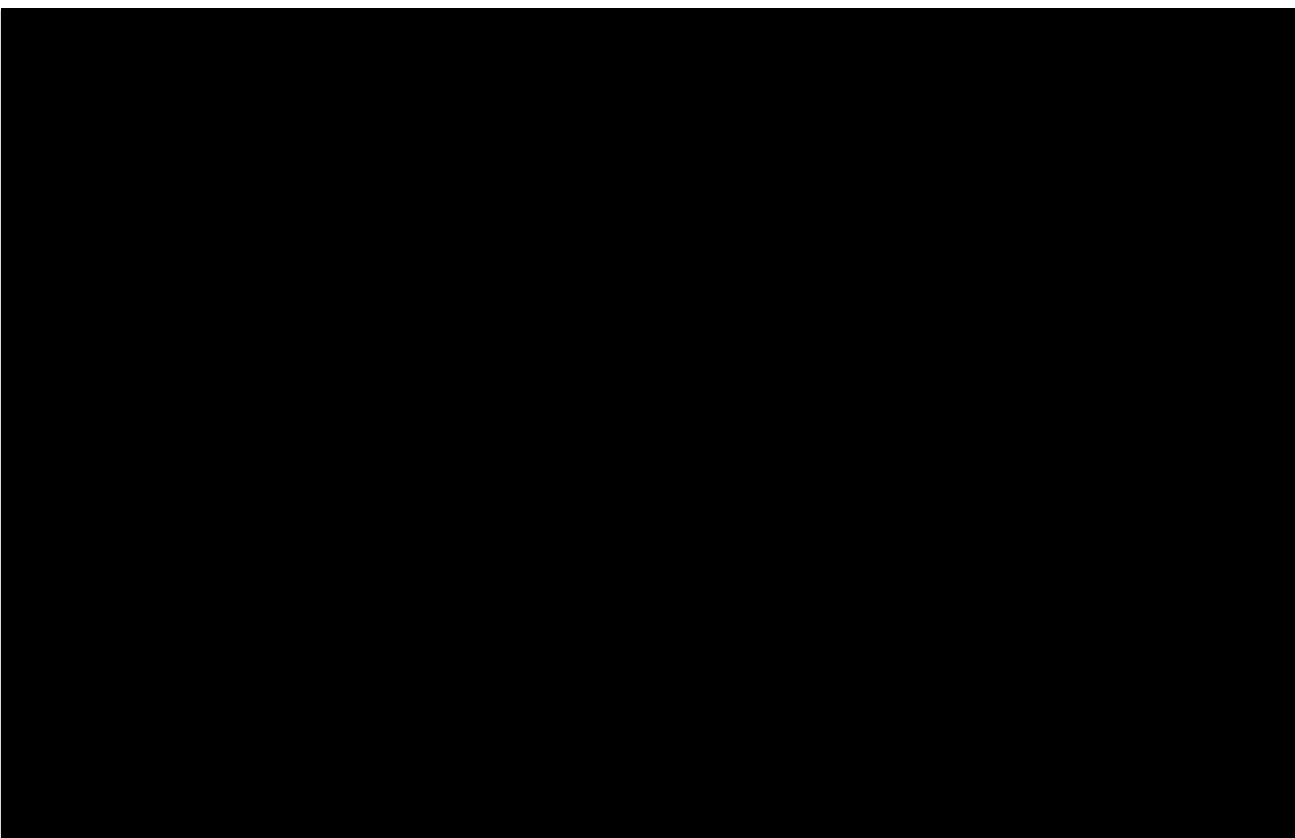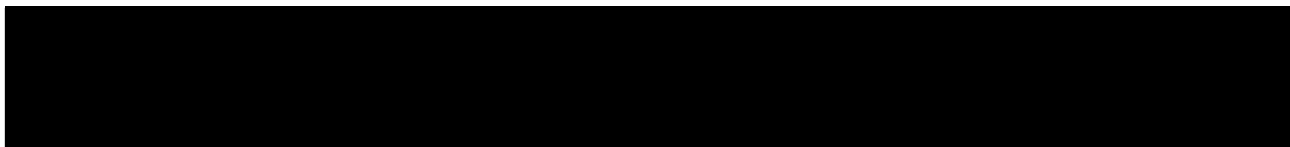
9   CONTENT OF REPORTS

9.1   Planned Analyses

- The analysis for the primary endpoint will be performed after all subjects have reached post-treatment Week 12 (SVR12) ;
- The final analysis (SVR24) will be performed at study completion.

9.2   Listings

Refer to Core SAP Section 9.2.
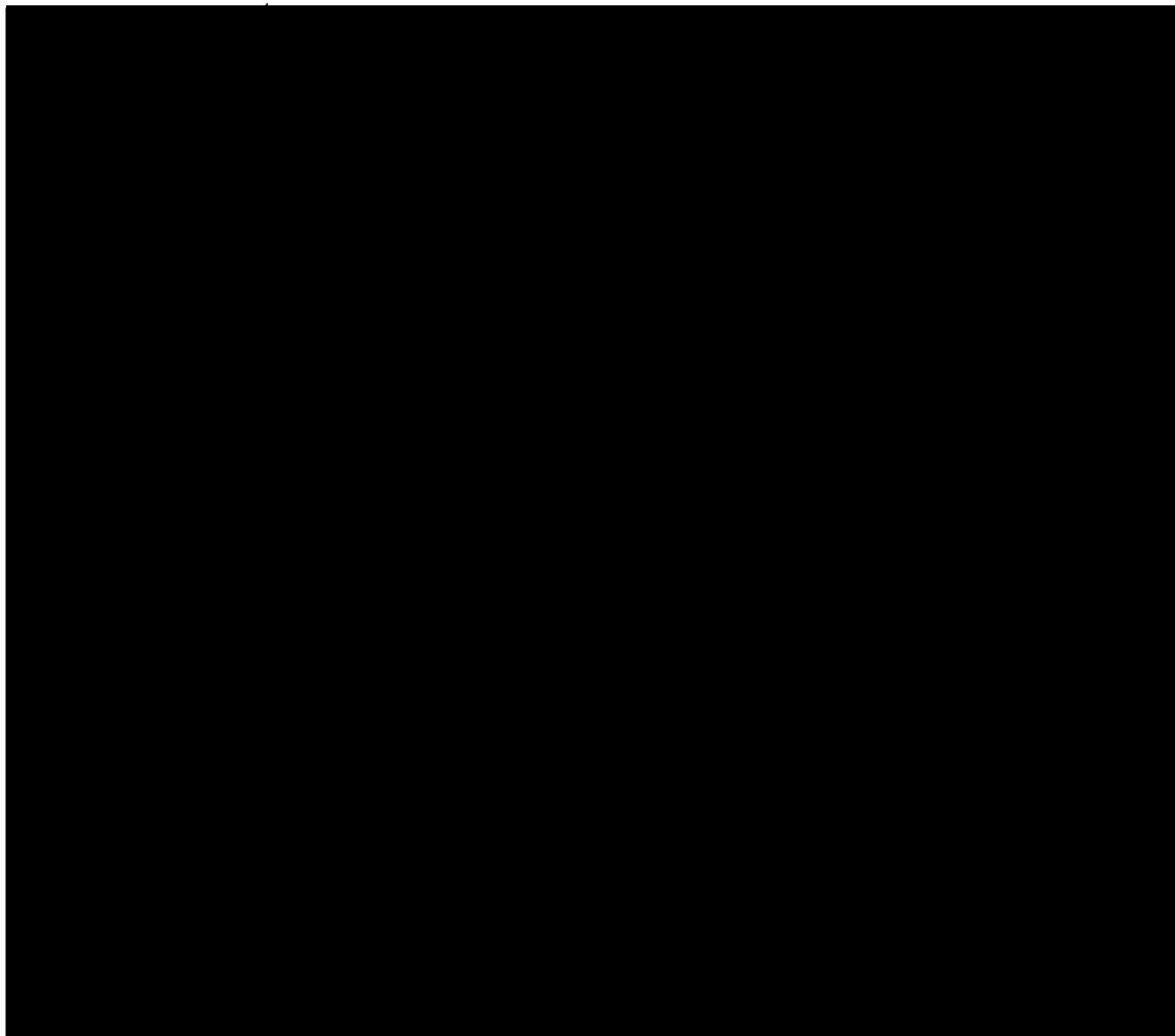
10   REFERENCES

For other references, see Core SAP Section 11.

APPENDIX 1   RELEVANT PROTOCOL DEVIATIONS

The relevant protocol deviations that can be programmed from the database are identified below.

The list would be updated as appropriate if, in the course of monitoring the study, additional protocol deviations are found and considered relevant.

APPENDIX 2   STANDARD ERROR ESTIMATE OF THE MEDIAN

Refer to Core SAP Appendix 2.

DOCUMENT HISTORY

Version Number	Author(s)	Description
1.0	███████████████	Initial version