

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207931Orig1s000

STATISTICAL REVIEW(S)

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 207931

Applicant: AbbVie **Stamp Date:** Feb. 25, 2015

Drug Name: Technivie (Ombitasvir, Paritaprevir, Ritonavir [12.5 mg/75 mg/50 mg], referred as 2-DAA hereafter)

NDA/BLA Type: NDA, priority Review

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	✓			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	✓			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- The currently submitted dataset for HCV RNA viral load is derived (i.e., ETD.XPT). Please provide the raw HCV RNA data and the corresponding SAS program to convert the raw HCV RNA data to the derived data.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	✓			The study report for Study M13-393 included in the NDA is the interim clinical study report.
Appropriate references for novel statistical methodology (if present) are included.			✓	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Brief summary of controlled clinical trials

The following table contains information on the relevant trials contained in the submission.

Study number	Design	Patient population ¹	Treatment arms/ Sample size ²	Primary efficacy endpoint	Sponsor's findings
M13-393 (PEARL-1)	phase 2, multicenter, randomized, open-label	treatment-naïve (TN) or pegIFN/ribavirin (RBV) treatment-experienced (TE) noncirrhotic subjects infected with genotype (GT) 4 HCV; or TN or pegIFN/RBV TE cirrhotic and noncirrhotic subjects infected with GT1b HCV	<p>The following three groups are for GT4 subjects:</p> <p>Group 1: 12-week 2-DAA for GT4 TN subjects, n=44</p> <p>Group 4: 12-week 2-DAA + RBV for GT4 TN subjects, n=42</p> <p>Group 6: 12-week 2-DAA + RBV for GT4 TE subjects, n=49</p> <p>The following four groups are for GT1b subjects:</p> <p>Group 2: 12-week 2-DAA for GT1b TN subjects, n=42</p> <p>Group 3: 12-week 2-DAA for GT1b TE null responders, n=40</p> <p>Group 7: 24-week 2-DAA for GT1b TN subjects, n=47</p> <p>Group 8: 24-week 2-DAA for GT1b TE subjects, n=52</p>	SVR12 defined as sustained virologic response (HCV RNA < lower limit of quantification) 12 weeks after the last dose of study drug	Please see tables in next two pages which display the sponsor's findings for the primary efficacy endpoint.

¹ In the submission, the sponsor was to seek the approval of 2-DAA in treatment of GT4 HCV infection only.

² Group 5 was originally planned to enroll GT4 TE subjects to receive 2-DAA for 12 weeks. However, according to the sponsor, Group 5 was not opened for enrollment based on a protocol-specified interim review of results from the GT4 TN Groups 1 and 4.

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Primary efficacy endpoint for GT4 Groups (ITT population)

Assessment	HCV GT4 Group			
	12 Wks 2-DAA	12 Wks 2-DAA + RBV		
	Group 1 T-Naïve N = 44	Group 4 T-Naïve N = 42	Group 6 T-Exp-All N = 49	Groups 4 + 6 N = 91
SVR ₁₂ ^a , n/N (%)	40/44 (90.9)	42/42 (100.0)	49/49 (100.0)	91/91 (100.0)
95% CI ^b	78.3, 97.5	91.6, 100.0	92.7, 100.0	96.0, 100.0
Nonresponse ^c , n/N (%)	4/44 (9.1)	0/42	0/49	0/91
Reason for nonresponse, n/N (%)				
On-treatment virologic failure	1/44 (2.3)	0/42	0/49	0/91
Rebound ^d	1/44 (2.3)	0/42	0/49	0/91
Fail to suppress ^e	0/44	0/42	0/49	0/91
Relapse ₁₂ ^f	2/42 (4.8)	0/42	0/49	0/91
Premature study drug discontinuation ^g	1/44 (2.3)	0/42	0/49	0/91

2-DAA = ABT-450 150 mg + ritonavir 100 mg + ABT-267 25 mg; CI = confidence interval; DAA = direct-acting antiviral agent; GT = genotype; ITT = intent-to-treat; LLOQ = lower limit of quantification; RBV = ribavirin; SVR = sustained virologic response; T-Exp-All = all treatment-experienced with pegylated-interferon/RBV (includes partial and null responders and relapsers); T-Naïve = treatment-naïve; Wks = weeks

- SVR₁₂ = HCV RNA < LLOQ in the SVR₁₂ window (12 weeks after last actual dose of study drug) without any confirmed quantifiable post-treatment value before or during that SVR window.
- Confidence interval constructed using the Clopper-Pearson exact method.
- Nonresponse = did not achieve SVR₁₂.
- Rebound = confirmed HCV RNA ≥ LLOQ (after < LLOQ during treatment), or confirmed increase from nadir (2 consecutive HCV RNA measurements > 1 log₁₀ IU/mL above nadir) at any time point during treatment.
- Fail to suppress = never achieved HCV RNA < LLOQ during at least 6 weeks of treatment (study drug duration ≥ 36 days).
- Relapse₁₂ = confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR₁₂ assessment time point) for a subject with HCV RNA < LLOQ at final treatment visit who completes treatment (defined as study drug duration ≥ 77 days for subjects in Substudy 1 and ≥ 154 days for subjects in Substudy 2).
- Prematurely discontinued study drug with no on-treatment virologic failure

Source: Table 22 in M13-393 Clinical Study Report

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Primary efficacy endpoint for GT1b Groups (ITT population)

	HCV GT1b Group					
	Noncirrhotic (12 Wks 2-DAA)			Cirrhotic (24 Wks 2-DAA)		
	Group 2 T-Naïve N = 42	Group 3 T-Exp-Null N = 40	Groups 2 + 3 N = 82	Group 7 T-Naïve N = 47	Group 8 T-Exp-All N = 52	Groups 7 + 8 N = 99
SVR ₁₂ ^a , n/N (%)	40/42 (95.2)	36/40 (90.0)	76/82 (92.7)	46/47 (97.9)	50/52 (96.2)	96/99 (97.0)
95% CI ^b	83.8, 99.4	76.3, 97.2	84.8, 97.3	88.7, 99.9	86.8, 99.5	91.4, 99.4
Nonresponse ^c , n/N (%)	2/42 (4.8)	4/40 (10.0)	6/82 (7.3)	1/47 (2.1)	2/52 (3.8)	3/99 (3.0)
Reason for nonresponse, n/N (%)						
On-treatment virologic failure	0/42	1/40 (2.5)	1/82 (1.2)	0/47	0/52	0/99
Rebound ^d	0/42	1/40 (2.5)	1/82 (1.2)	0/47	0/52	0/99
Fail to suppress ^e	0/42	0/40	0/82	0/47	0/52	0/99
Relapse ₁₂ ^f	0/42	3/39 (7.7)	3/79 (3.8)	0/44	1/52 (1.9)	1/96 (1.0)
Premature study drug discontinuation ^g	1/42 (2.4)	0/40	1/82 (1.2)	1/47 (2.1)	0/52	1/99 (1.0)
Missing SVR ₁₂ data	1/42 (2.4)	0/40	1/82 (1.2)	0/47	1/52 (1.9)	1/99 (1.0)

2-DAA = ABT-450 150 mg + ritonavir 100 mg + ABT-267 25 mg; DAA = direct-acting antiviral agent; GT = genotype; ITT = intent-to-treat; LLOQ = lower limit of quantification; RBV = ribavirin; SVR = sustained virologic response; T-Exp-All = all treatment-experienced with pegylated-interferon/RBV (includes partial and null responders and relapsers); T-Exp-Null = treatment-experienced with pegylated-interferon/RBV-null responders only; T-Naïve = treatment-naïve; Wks = weeks

- a. SVR₁₂ = HCV RNA < LLOQ in the SVR₁₂ window (12 weeks after last actual dose of study drug) without any confirmed quantifiable post-treatment value before or during that SVR window.
- b. Confidence interval constructed using the Clopper-Pearson exact method.
- c. Nonresponse = did not achieve SVR₁₂.
- d. Rebound = confirmed HCV RNA ≥ LLOQ (after < LLOQ during treatment), or confirmed increase from nadir (2 consecutive HCV RNA measurements > 1 log₁₀ IU/mL above nadir) at any time point during treatment.
- e. Fail to suppress = never achieved HCV RNA < LLOQ during at least 6 weeks of treatment.
- f. Relapse₁₂ = confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR₁₂ assessment time point) for a subject with HCV RNA < LLOQ at final treatment visit who completes treatment (defined as study drug duration ≥ 77 days for subjects in Substudy 1 and ≥ 154 days for subjects in Substudy 2).
- g. Prematurely discontinued study drug with no on-treatment virologic failure.

Source: Table 24 in M13-393 Clinical Study Report

Karen Qi	03/23/2015
Reviewing Statistician	Date
Greg Soon	03/23/2015
Secondary Reviewer	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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04/22/2015

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04/24/2015