CELLTRION Inc.

CT-P13 3.5

A Randomized, Parallel-Group, Phase I/III Study to Evaluate Efficacy, Pharmacokinetics and Safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients with Active Rheumatoid Arthritis

15th July 2019

Statistical Analysis Plan Addendum

Part 2 – Final Version 4.0 Addendum Version 1.0

Prepared by:

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Prepared by: _____ Date: ____/____/____

[redacted]

Approved by: _____ Date: ____/____/____

[redacted]

The undersigned agree to the changes to the statistical analyses and procedures outlined in this Statistical Analysis Plan Addendum.

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1. Statistical Analysis Plan Addendum

The Statistical Analysis Plan (SAP) Addendum details the revision that are not currently described in the CT-P13 3.5 Part 2 SAP final Version 4.0 dated 24 March 2019.

2. Overview of Changes Required

This SAP addendum describes that all analyses will be performed by excluding the patients from the significant GCP non-compliance site for final Clinical Study Report (CSR).

2.1. Change of Section 5.6. Protocol Deviations

Regardless of when deviation is recognized, patients from significant GCP non-compliance site will be excluded from all populations. Since those patients will be excluded from all analyses, corresponding sensitivity analyses for primary endpoint (Table 14.2.2.1S and Table 14.2.2.1BS) will not be performed. The statement of SAP is modified as follows.

- Significant GCP non-compliance (All populations): CELLTRION will identify the sites which have been closed or patients who have been affected due to suspected scientific misconduct and/or serious GCP non-compliance. **~~Some analysis population can be determined based on the details of the significant GCP non-compliance found after unblinding. Affected population will be discussed and determined during DRM and population to exclude the patients with significant GCP non-compliance will be specified in listing. In addition, a sensitivity analysis (Section 10.1.4.2) will be conducted considering the significant GCP non-compliance sites.~~**

  Based on the discussion at Week 54 DRM, [redacted] with Confirmed Scientific Misconduct issue was identified to significant GCP non-compliance.~~ Based on the discussion at Week 54 DRM, patients from [redacted] with Confirmed Scientific Misconduct issue will be excluded from the usability population only. The other populations will include the [redacted], and sensitivity analysis will be additionally performed for the primary analysis excluding the patients from the [redacted].~~

2.2. Change of Section 10. EFFICACY ANLAYSIS

As patients from significant GCP non-compliance site are excluded from all analyses, corresponding sensitivity analyses are not required. Therefore the following sentence is deleted.

If significant GCP non-compliance is identified after unblinding, an additional sensitivity analysis will be performed for primary efficacy analysis on DAS28 (CRP) at Week 22. It will be conducted by considering GCP non–compliance sites on both Efficacy and All-Randomized populations.

2.3. Change of Section 10.1.4.2 Sensitivity Analysis

The following sentence is deleted for the same reason as above.

If significant GCP non-compliance is identified after unblinding, the ANCOVA will be performed for DAS28 (CRP) at Week 22 by considering GCP non–compliance sites on both Efficacy and All-Randomized populations.

2.4. Change of Table and Listing in Shell

As patients from significant GCP non-compliance site are excluded from all analyses, Table 14.2.2.1S and Table 14.2.2.1BS will not be generated and shell related this issue is modified as follows.

- **Table 14.1.3 Major Protocol Deviations:**

	SC 120mg (N=XX)	IV 3mg/kg (N=XX)	Total (N=XX)	Excluded Populations [1]
Major Protocol Deviation				
Mis-randomizations	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	EFF, PK
Non-compliance of I/E criteria associated with efficacy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	EFF
Receipt of joint surgery, synovectomy or intra-articular injection before Week 22	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	EFF
Significant GCP non-compliance ~~found after unblinding~~	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	**ALL~~USA~~**
Dose Skip	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	EFF

Note: Percentages are calculated by using the number of patients in the All-Randomized population as the denominator. ~~**Based on the discussion at Week 54 DRM, patients from [redacted] with Confirmed Scientific Misconduct issue are excluded from the usability population only.**~~
I/E criteria = Inclusion or Exclusion criteria, ALL = All populations, EFF = Efficacy population, PK = Pharmacokinetic population~~,~~ ~~**USA = Usability population**~~.
[1] Protocol deviation excludes patients from the following population.

- **Listing 16.2.2.2: Major Protocol Deviations**

Patient No.	Age/Sex/Race	Type of Deviation	Description	Excluded Populations [1]
XXXX-XXXX	XX/X/X	Mis-randomizations	XXXXXXXXXXXXXXXXXX	EFF, PK
XXXX-XXXX	XX/X/X	Non-compliance of I/E criteria which affect efficacy result	XXXXXXXXXXXXXXXXXX	EFF
		Receipt of joint surgery, synovectomy or intra-articular injection before Week 22	XXXXXXXXXXXXXXXXXX	EFF
		Significant GCP non-compliance	XXXXXXXXXXXXXXXXXX	ALL
		~~**Significant GCP non-compliance found after unblinding**~~	~~**XXXXXXXXXXXXXXXXXX**~~	~~**USA**~~
		Dose Skip	XXXXXXXXXXXXXXXXXX	EFF

Note: M = Male, F = Female. A = Asian/Oriental, W = Caucasian/White, B = African/Black, N = Not allowed by Investigator country regulations, O = Other, I/E criteria = Inclusion or Exclusion criteria.
[1] Major protocol deviations exclude patients from one or more of the following populations.
ALL = All populations, EFF = Efficacy population, PK = Pharmacokinetic population, ~~**USA = Usability population,**~~ N/A = Not Applicable.

- **Listing 16.2.6.3 DAS28 and EULAR Response Categories:** "* = Patient from GCP non-compliance site found after unblinding. The data of this patient were excluded in the additional sensitivity analysis." and "*" flag in the listing are deleted.