Paper SA08

Interaction with FDA during and after a Type C meeting from the perspective of a statistical Programmer.

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ABSTRACT

The Type C meeting was used to coordinate the electronic submission requirements for a pediatric submission in type 2 diabetes mellitus with the FDA. The planned deliverables were detailed in an esub (electronic submission) plan. FDA's response to that esub plan was quite different to what was proposed concerning the programs for analysis datasets, tables, listings and graphs as well as analysis results metadata. They also detailed specific requirements for the datasets including laboratory units that we did not meet. They asked for a specific listing of the main statistical analyses that we had not foreseen. The details of the BIMO package required extensive discussions with FDA.

It will be explained how constructive communication with the FDA after the Type C meeting can lead to a clear understanding of the electronic submission requirements and thereby avoid much unnecessary work and alleviate the risk of rejection.

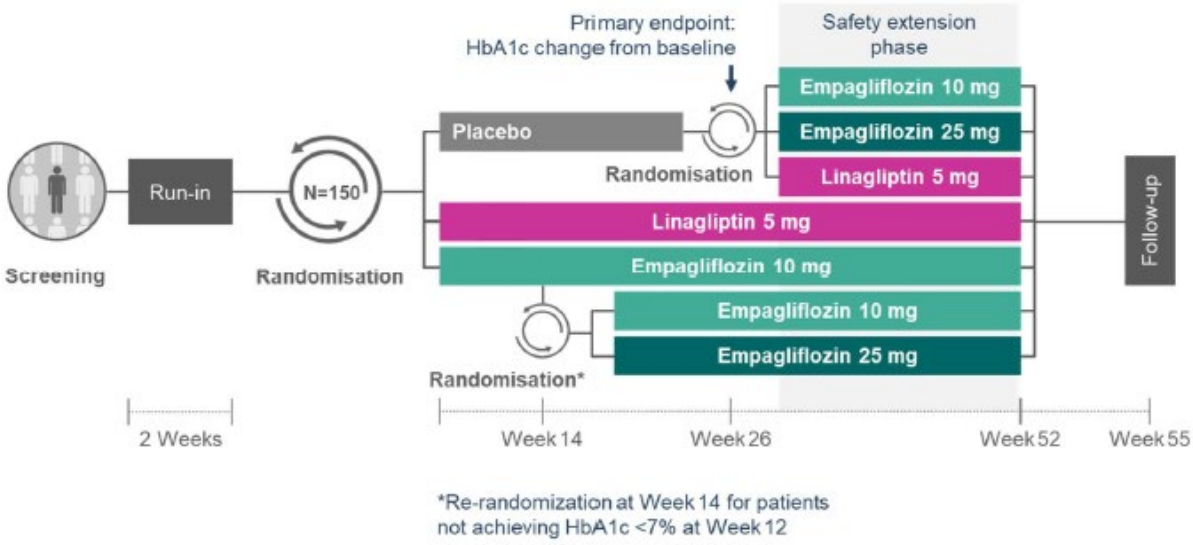
INTRODUCTION AND OBJECTIVES

In the specific case, the esub plan proposed to deliver analysis data sets in the form of ADaM (Analysis Data Model) data sets along with the appropriate data set programs, define.xml, and ADRG (Analysis Data Reviewer's Guide) for the pivotal study. It was proposed to provide pooled ADaM datasets without dataset programs but with define.xml and ADRG for the SCS (Summary of Clinical Safety) including another study in the same indication. It was also offered to submit the analysis program for the primary endpoint of the pivotal study. The proposed deliverables are shown in the table below.

Topic	Proposed Deliverables
Report	Analysis program of the primary endpoint of the pivotal study
ADaM	Analysis datasets of the pivotal study and pooled analysis datasets for the SCS (Summary of Clinical Safety) for the pivotal study and another study
ADaM	Programs for the ADaM (Analysis Data Model) datasets of the pivotal study
ADaM	Define.xml for the pivotal study including ARM (Analysis Results Metadata) of the primary endpoint and define.xml for the SCS
ADaM	One ADRG (Analysis Datasets Reviewers Guide) for the pivotal study and the SCS each
BIMO	BIMO (Bioresearch Monitoring) package of the pivotal study

A diagram of the pivotal study DINAMO™ is shown below. The primary endpoint was: HbA1c [%] change from baseline at week 26, ANCOVA – multiple imputation with wash-out approach.

a) DINAMO™



MAIN CHALLENGES AND SOLUTIONS

THE FDA RESPONSE TO THE PROPOSAL TO PROVIDE THE ANALSIS PROGRAM OF THE PRIMARY ENDPOINT ONLY WAS AS FOLLOWS:

- **Provide clear and well commented analysis programs that you utilized to produce all major tables, graphs, and results for both safety and efficacy.**
- **All macros inside the actual program for running should also be submitted.**

AS A RESPONSE TO THE FDA REQUEST:

- 28 tables of the pivotal study were proposed to the FDA as major tables, graphs, and results for both safety and efficacy
  - 1 Disposition table
  - 1 Exposure table
  - 14 Efficacy tables
  - 12 Adverse event (AE) tables

- 14 tables of the SCS were proposed to the FDA as major tables, graphs, and results for both safety and efficacy
  - 2 Disposition table
  - 2 Exposure tables
  - 10 AE tables

After acceptance of the proposed analyses by the FDA a tabular listing of these analyses were prepared in the ADRGs, of which examples are shown below.

Examples from the tabular listing for the major tables and outcomes of the pivotal study

Program Name	Major Table and Outcome	Datasets used	Macros used for calculation
csd-tdisp-tg1.sas	Table 15.1.1: 1 Disposition of patients by randomised treatment group at the initial randomisation – SCR (TG1)	ADSL	***%X_TLF_DISP1***
csd-texpo-overall-ptyr-tg1.sas	Table 15.1.5: 1 Exposure to study medication up to Wk26 – TS (TG1)	ADSL, ADEXCOMP	***%X_TLF_DESC1***
csd-ancova-chg-hba1c-tg1.sas	Table 15.2.1.1.1: 1 HbA1c [%] change from baseline at Week 26 – multiple imputation with wash–out approach – mITT (TG1) (OC–AD)	ADSL, ADHBA1C	***none***

- BI (Boehringer Ingelheim) specific CSD (Company Standard Display) macros were used to produce these major tables, graphs, and results. These macros were only available as compiled macros, so that they had to be adapted to run outside the BI specific reporting environment in a SAS session. These CSD macros are very large because they were programmed for both calculations and layout generation and cover a wide range of analyses. To confirm our approach, an AE reporting program together with the CSD macro program, the required analysis datasets, and the corresponding output table was sent to the FDA. In the reply it became clear that more details were needed:

  We were able to run your codes and were able to reproduce your provided safety tables. Of note, your macro program contains a lot of code lines and has almost no comments or clarifications […] We need well-commented codes that provide step by step instructions.

  In order to fulfill the FDA requirement a submission support memo was written for the CSD macros with explanations how the setting of macro parameters could be chosen in a macro call in order to:
  - Display the program flow of the macro modules in the LOG window
  - Save all temporary datasets
  - Identify the module that does the calculation step
  - Display the code that does the calculation in the LOG window

  The previously provided AE reporting program package was provided again together with the submission support memo and the CSD user manual to the FDA for acceptance. A question was added if for layout generation the same level of detail would be required. Finally, the FDA accepted this approach:

  Yes, your detailed explanation with the company standard displays (CSD) user manual and the submission support memo are acceptable.
  No, we do not need details for mere layout generation of the reports.

THE FDA RESPONSE TO THE PROPOSAL TO PROVIDE ANALSIS DATASETS OF THE PIVOTAL STUDY AND OF THE SCS WAS AS FOLLOWS:

- **Your analysis datasets should include all variables needed for conducting all primary, secondary, sensitivity, and safety analyses included in the study report.**
- **We request that you provide laboratory data and analyses in conventional units in addition to standardized SI units to facilitate our review.**

AS A RESPONSE TO THE FDA REQUEST:

- It was confirmed with the FDA that the multiple imputation approach (500 imputations) for the primary endpoint was implemented in the analysis program of the primary endpoint but not available as an ADaM dataset.
- A separate lab dataset ADLBUSC was created with US conventional units that were confirmed with the FDA.

THE FDA RESPONSE TO THE PROPOSAL TO PROVIDE ANALSIS DATASET PROGRAMS OF THE PIVOTAL STUDY BUT NOT FOR THE SCS AND A DEFINE.XML FOR BOTH THE PIVOTAL STUDY AND THE SCS WAS AS FOLLOWS:

- **Provide the location of the dataset, the names of the variables used, and the programs used to get every new value that will be appearing in the label.**
- **Also, separately, provide the specific codes that were used to create your ADAM datasets.**

AS A RESPONSE TO THE FDA REQUEST:

- The information on dataset locations as well as the program names to create the datasets was provided in the define.xml with direct links to the datasets and the programs submitted. All variables as well as their derivations were detailed in the define.xml. In the ADRG further explanations were added as needed.
- As ADaM datasets for the extra study in the SCS had been submitted previously, the FDA confirmed that we did not need to supply the programs for SCS dataset generation.

THE FDA RESPONSE TO THE PROPOSAL TO PROVIDE ANALYSIS RESULTS METADATA OF THE PRIMARY ENDPOINT ANALYSIS ONLY WAS AS FOLLOWS:

- **Include the analysis results metadata in define.xml that specify the programming statements and selection criteria needed to recreate individual tables, listings, and figures.**
- **Provide a separate tabular listing to describe the key statistical analysis you have done.**

AS A RESPONSE TO THE FDA REQUEST:

- 13 key statistical tables were selected and confirmed with the FDA, of which analysis results metadata were to be provided in the define.xml. For each table separate entries were created for the different statistical analyses (see below).

Analysis Results Metadata - Summary

Table 15.2.1.1.1: 1 HbA1c [%] change from baseline at Week 26 - multiple imputation with wash-out approach - mITT (TG1) (OC-AD)
- Adjusted mean / SE of HbA1c absolute values at week 26 using ANCOVA
- Pairwise treatment comparisons against Placebo using ANCOVA

Table 15.2.1.1.2: 1 HbA1c [%] change from baseline at Week 26 - multiple imputation with wash-out and inverse probability weighting approach - mITT (TG2) (OC-AD)
- Adjusted mean / SE of HbA1c absolute values at week 26 using ANCOVA
- Pairwise treatment comparisons against Placebo using ANCOVA

Analysis results metadata of the adjusted mean

Table 15.2.1.1.1: 1

Display	**HbA1c [%] change from baseline at Week 26 - multiple imputation with wash-out approach - mITT (TG1) (OC-AD)**
Analysis Result	**Adjusted mean / SE of HbA1c absolute values at week 26 using ANCOVA**
Analysis Parameter (s)	PARAMCD = "HBA1C" (Hemoglobin A1C [%])
Analysis Variable (s)	ADHBA1C.AVAL (Analysis Value)
Analysis Reason	SPECIFIED IN SAP
Analysis Purpose	PRIMARY OUTCOME MEASURE
Data References (incl. Selection Criteria)	ADHBA1C [AGEGR1 ^= " " and ANL02FL = "Y" and BASETYPE = "STUDY" and MITTFL = "Y" and PARAMCD = "HBA1C"]
Documentation	Visit numbers between 15 (baseline) and 50 (week 26) were selected. For analysis of TG1 (OC-AD) CAT1 was set to TRPG1N (1=Placebo, 2=Linagliptin, 3=Empagliflozin Pooled). Join ADHBA1C with ADSL based on the unique subject identifier (USUBJID). Keep variables AGEGR1N, RAND14FL, TR03SDT, TRTEDY from ADSL for data building of multiple imputation. Adjusted means of HbA1c absolute values at week 26 based on an ANCOVA model with baseline HbA1c as a continuous model term, and with categorical terms for treatment and age at randomisation for the 500 complete imputations (see external documentation: TSAP Section 7.4.1.1 for imputation rules and ADRG Section 6.4.1 for the programming of multiple imputation datasets). Rubin's rules were used to combine treatment effect estimates across the 500 complete imputations. Analysis Data Reviewers Guide [57]

Programming Statements	[SAS version 9.4]
	`%* For data building of multiple imputation dataset _x_mi1 see ADRG 6.4.1;`
	`%** ANCOVA with each of 500 datasets for adjusted week 26 HbA1c absolute values;`
	`footnote 'trpg1n: 1 = Pbo, 2 = L5, 3 = E Pooled';`
	`ODS listing close;`
	`proc mixed data=_x_mi1;`
	`  by _Imputation_;`
	`  class  trpg1n (ref="1") agegr1n;`
	`  model  aval_wk26 = hba1cbl trpg1n agegr1n / ddfm=kr solution;`
	`  lsmeans trpg1n / diffs cl om alpha=0.05;`
	`  ods output lsmeans=_x_mi1_lsm_aval;`
	`run;`
	`ODS listing;`
	
	`%** combine ANCOVA results using Rubins rule;`
	`proc mianalyze parms(classvar=full)=_x_mi1_lsm_aval;`
	`  class trpg1n;`
	`  modeleffects trpg1n;`
	`  ods output ParameterEstimates=_x_mian1_lsm_aval;`
	`run;`
	TLF program: csd-ancova-chg-hba1c-tg1

- A tabular listing of the confirmed 13 key statistical tables was provided in the ADRG according to the instructions provided by the FDA (see below).

Excerpt from the tabular listing of the key statistical analyses

Output file name	Program Name	Title / Description	Datasets used	Macros used for reporting
15_2_1_1_1_1_CSD-ANCOVA-CHG-HBA1C_1_T.lst	csd-ancova-chg-hba1c-tg1.sas	Primary efficacy analysis in CTR Appendix Table 15.2.1.1.1: 1 HbA1c [%] change from baseline at Week 26 – multiple imputation with wash–out approach – mITT (TG1) (OC–AD)	ADSL, ADHBA1C	%*X_TLF_ANCOVA1*
15_2_1_1_2_1_CSD-ANCOVA-CHG-HBA1C_2_T.lst	csd-ancova-chg-hba1c-tg2.sas	Primary efficacy analysis in CTR Appendix Table 15.2.1.1.2: 1 HbA1c [%] change from baseline at Week 26 – multiple imputation with wash–out and inverse	ADSL, ADHBA1C	%*X_TLF_ANCOVA1*

FILLING THE ARM VARIABLE OF THE CLINSITE DATASET:

The FDA uses the numbers from the CLINSITE dataset to check against the numbers from the CTR (Clinical Trial

Report). The 8 possible treatment sequences of the DINAMO™ trial that cover the whole trial period (see below) were not suitable to populate the ARM variable because they were not used as such for analysis in the CTR. Instead, it was agreed to consider the 3 treatments of the original randomization until week 26 in the ARM variable as 'TG1-censored' representing the primary safety and efficacy analysis of the CTR (see below). In order to cover the whole trial analysis period, it was agreed to consider the 3 treatments of the original randomization in the ARM variable as 'TG1-extended' (see below) in addition.

8 treatment sequences from the ARM variable of DM and ADSL datasets

PBO (stopped before re-randomization at week 26)
PBO-EMPA 10mg (re-randomized at week 26)
PBO-EMPA 25mg (re-randomized at week 26)
PBO-LINA 5mg (re-randomized at week 26)
LINA 5mg
EMPA 10mg
EMPA 10mg-EMPA 10mg (re-randomized at week 14)
EMPA 10mg-EMPA 25mg (re-randomized at week 14)

3 treatment arms representing the original randomization and analysis until week 26 as used in the ARM variable.

'TG1-censored-Placebo',
'TG1-censored-Lina',
'TG1-censored-Empa pooled'.

3 treatment arms representing the original randomization and analysis over the whole trial period as used in the ARM variable.

'TG1-extended-Placebo',
'TG1-extended-Lina',
'TG1-extended-Empa pooled'.

CONCLUSIONS

The extensive communication with the FDA through advice request letters after the Type C meeting led to a clear understanding of the specific electronic submission requirements for the DINAMO™ trial. Specific proactive proposals to the FDA for major tables, graphs and results, key statistical analyses or the non-conventional filling of the ARM variable in the BIMO package were accepted by the FDA. Detailed explanations as with the use of the CSD macros ultimately led to the acceptance of the proposal, even if it was initially met with skepticism. Communicating with the FDA pays off by minimizing the risk of a submission being rejected. Indeed, our submission was accepted by the FDA. Nevertheless, despite the extensive communication surprisingly the CLINSITE dataset of the BIMO package had to be adapted to the technical conformance guide version 2 from version 1 shortly before submission. Finally, enough response time for raising and answering all the questions needs to be planned for. In addition, close collaboration between Data Management, Statistics, and Programming, as well as Regulatory departments are essential.

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