

Presentation SA08

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

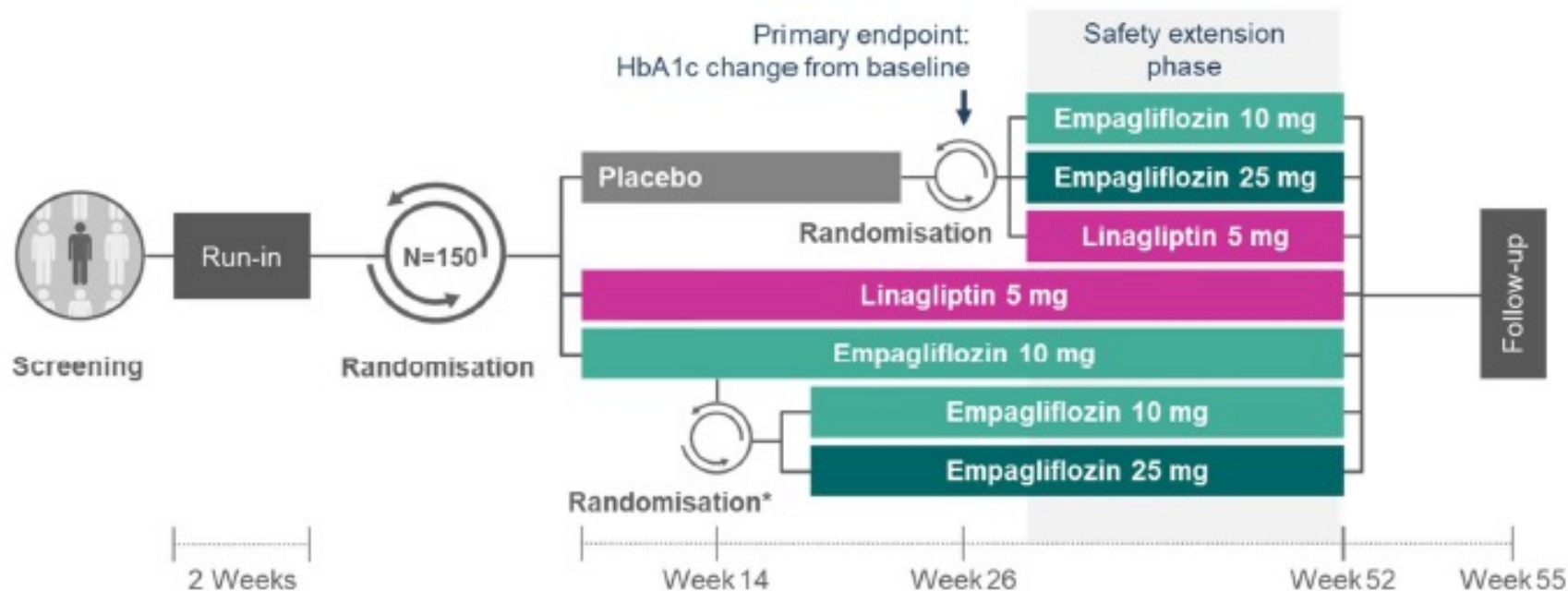
Dieter Hartz, PHUSE EU Connect, 2023

The Type C meeting was used to coordinate the electronic submission deliverables for a pediatric submission in type 2 diabetes mellitus with the FDA. Part of the briefing package was a so called esub (electronic submission) plan, that was prepared by both Data management and Programming and contained the details of deliverables, i.e. which data, programs, outputs etc. were planned to be submitted.

The planned deliverables from Programming are shown as follows.

Topic	Planned Deliverables
Report	Analysis Program of the Primary Endpoint of the pivotal Study
ADaM	Analysis Datasets of the pivotal Study and pooled Analysis Datasets of the SCS (Summary of Clinical Safety) including another Study
ADaM	Programms for ADaM (Analysis Data Model) Datasets of the pivotal Study
ADaM	Define.xml for the pivotal Study incl. ARM (Analysis Results Metadata) for the primary Endpoint and Define.xml for the SCS
ADaM	ADRG (Analysis Datasets Reviewers Guide) for the pivotal Study and for the SCS each
BIMO	BIMO (Bioresearch Monitoring) Package for the pivotal Study

a) DINAMO™



*Re-randomization at Week 14 for patients not achieving HbA1c <7% at Week 12

Primary endpoint: HbA1c [%] change from baseline at Week 26, ANCOVA - multiple imputation with wash-out approach

Topic	FDA Answer from Type C Meeting
Reports	➤ Provide clear and well commented analysis programs that you utilized to produce all major tables, graphs, and results for both safety and efficacy. ➤ Provide a separate tabular listing to describe the key statistical analysis you have done.
	BI Action
	Together with the Statistician 28 tables of the pivotal study (see below) und 14 tables of the SCS were selected and proposed to the FDA. ➤ 1 Disposition table ➤ 1 Exposure table ➤ 14 Efficacy tables incl. 13 key efficacy tables ➤ 12 Adverse event tables
	FDA Answer:
	➤ acceptable

Examples: Major Tables and Outcomes

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	<i>%X_TLF_DISP1</i>
csd-texpo-overall-ptyr-tg1.sas	Table 15.1.5: 1 Exposure to study medication up to Wk26 – TS (TG1)	ADSL, ADEXCOMP	<i>%X_TLF_DESC1</i>
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	<i>none</i>

Examples: Key Statistical Analysis and Outcomes

Output file name	Program Name	Title / Description	Datasets used	Macros used for reporting
15_2_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	<i>%X_TLF_ANCOVA1</i>
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	ADSL, ADHBA1C	<i>%X_TLF_ANCOVA1</i>

Type C Meeting, written Answer from the FDA cont.

Use of BI specific CSD Macros

FDA Answer from Type C Meeting

- All macros inside the actual program for running should also be submitted.

BI Action

Because compiled BI (Boehringer Ingelheim) specific CSD (Company Standard Displays) macros were used to produce these tables they needed adaptation so that they they could be run outside the BI-specific reporting environment. The CSD macro programs are very large because they are intended for calculations and data output in specific layout.

- 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.

 csd-tae-tfrq-trisk.txt 11 KB	 loadSource-xtlfhiea0102C.txt 1 MB	 1218-0091-sample-study-report-body.pdf 37 KB	 ADAE.xpt 9 MB
 ADEXCOMP.xpt 6 MB	 ADSL.xpt 1 MB		

FDA Answer

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.

BI Action

A submission support memo was created with explanations of how the setting of macro parameters in the macro call could be set to:

- display the program flow of the used modules in the LOG window
 - save all temporary datasets
 - identify the module doing the calculation
 - Put out the code of the calculation module in the LOG window
- The previous package was sent again to the FDA together with the submission support memo as well as the CSD user manual for acceptance.
- It was also asked if for layout generation the same level of detail would be required.



CSD_User_Manual.pdf
4 MB



submission_support_memo.docx
708 KB



FDA Answer

- 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.



Topic	FDA Answer from Type C Meeting
ADaM Datasets	➤ 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.
	BI Action
	➤ The multiple imputation (500 imputations) for the primary endpoint was implemented in the analysis program of the primary endpoint but not available as ADaM dataset. Therefore, the FDA was asked for acceptance. ➤ A separate lab dataset ADLBUSC was created with US conventional units in addition to ADLB with SI (Système International) units. The FDA was asked for confirmation of these units.
	FDA Answer:
	➤ acceptable

Topic	FDA Answer from Type C Meeting
Dataset Programs / Define.xml	➤ Also, separately, provide the specific codes that were used to create your ADAM datasets. ➤ 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.
	BI Action
	➤ As ADaM datasets for the extra study in the SCS had been submitted previously the FDA was asked for confirmation that we did not need to supply the programs for SCS dataset generation. ➤ The information on the location of the datasets and the program names to create the datasets was provided in the define.xml with direct links to the datasets and programs submitted. All variables and their derivations were detailed in the define.xml. In the ADRG further explanations were added as needed.
	FDA Answer:
	➤ acceptable

Topic	FDA Answer from Type C Meeting
ARM / Define.xml	➤ Include the analysis results metadata in define.xml that specify the programming statements and selection criteria needed to recreate individual tables, listings, and figures.
	BI Action
	➤ Instead of ARM for the primary endpoint only, it was proposed to generate Analysis Results Metadata for the 13 key statistical tables (see example summary entries in the define.xml 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
	FDA Answer:
	➤ acceptable

Topic	BI Proposal for Filling the ARM Variable of the CLINSITE Dataset
BIMO	➤ For filling the ARM variable of the CLINSITE dataset a proposal was made to consider only the 3 treatments of the original randomization until week 26 ('TG1-censored') instead of the possible 8 treatment arms (treatment sequences) because this would reflect the primary safety and efficacy analysis of the study. In order to cover the whole study period it was proposed to consider the 3 treatments of the original randomization in the ARM variable as 'TG1-extended' in addition. 'TG1-censored-Placebo', 'TG1-censored-Lina', 'TG1-censored-Empa pooled'. 'TG1-extended-Placebo', 'TG1-extended-Lina', 'TG1-extended-Empa pooled'.
	FDA Answer ➤ Yes, we agree with the proposed ARM variable of the CLINSITE dataset for disposition, primary efficacy, and safety analysis as planned.

- Questions that arose after the FDA's response to the Type C meeting could be resolved through proactive suggestions in advice/information request letters.
- Providing detailed information may ultimately lead to acceptance of a proposal even if it was initially met with skepticism.
- Communication with the FDA pays off by minimizing the risk of a submission being rejected.
- Nevertheless, there can still be surprises during the submission. For example, the version for the BIMO package had to be adapted to the technical conformance guide version 2 from version 1 at short notice.
- Finally, enough response time for raising and answering all the questions needs to be planned for.

- **Dietmar Neubacher (STAT)**
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- **Tomasz Chlasciak (PROG)**
- **Angelika Boehm (PROG)**
- **Andreas Wegener (PROG)**
- **Addison Nguyen (Regulatory Affairs)**
- **Tamara Weber (Clinical Data Engineer)**

Dieter Hartz

Boehringer Ingelheim Pharma GmbH & Co. KG

Binger Str. 173

55216 Ingelheim am Rhein

Work Phone: +49 61 32 77 14 25 00

Email: dieter.hartz@boehringer-ingelheim.com

