Integrated

Analysis Data Reviewer’s Guide

QRS Pharmaceuticals

QRS-MED2022

Integrated Summary of Efficacy

iADRG Template Version 2022-04-DD

**<Disclaimer**: Any examples provided within this document should not be considered as the best practice for data pooling. Any questions from the sponsor should be directed to the agency review division.>

 **Integrated Analysis Data Reviewer’s Guide**

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# Introduction

## Purpose

This document provides context for the integrated analysis datasets and terminology that benefit from additional explanation beyond the Data Definition document (define.xml) for integrated studies and a summary of integrated analysis data conformance findings.

## Acronyms

| **Acronym** | **Translation** |
| --- | --- |
| ADaM | Analysis Dataset Model |
| ADRG | Analysis Data Reviewer’s Guide |
| iADRG | Integrated Analysis Data Reviewer’s Guide |
| BDS | Basic Data Structure |
| B-ALL  | B-cell lineage acute lymphoblastic leukemia |
| BMI | body mass index  |
| B-NHL | B-cell non-Hodgkin lymphoma |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DBL | Database Lock |
| DLBCL | diffuse large B-cell lymphoma |
| DLT | dose-limiting toxicity |
| FL | follicular lymphoma |
| IG | Implementation Guide |
| MCL | mantle cell lymphoma |
| MTD | maximum tolerated dose |
| NA | Not Applicable |
| RDE | recommended dose for expansion |
| SDTM | Study Data Tabulation Model |
| NCI | National Cancer Institute  |
| SAP | Statistical Analysis Plan |
| SCE | Summary of Clinical Efficacy |
| SMQ | Standardized MedDRA Query |
| TAUG | Therapeutic Area User Guide |

## Data Standards and Dictionary Inventory for Integrated Datasets

| **Standard or Dictionary** | **Versions Used** |
| --- | --- |
| SDTM Controlled Terminology | SDTM CT 2020-12-18 |
| ADaM | ADaM v2.1/IG 1.1OCCDS v1.0 |
| ADaM Controlled Terminology | ADaM CT 2020-11-06 |
| Data Definitions | Define.xml v2.0 |
| TAUG (if applicable) | Not Applicable |
| Medications Dictionary | WHODD Version Global B3 Mar2019 |
| Medical Events Dictionary | MedDRA v23.1 (includes COVID19 terminology) |
| Other standards  | CTCAE v5.0 |

**Additional Content of Interest**

No additional information

## Source Data Used for Integrated Analysis Dataset Creation

| **Study Identifier (STUDYID)** | **Protocol Number** | **Source Data Standard**  | **Cutoff-Date or DBL-Date****/ Study Status** |
| --- | --- | --- | --- |
| QRS01 | PRN-1001 | Legacy Analysis data (converted to ADaM IG v1.1) | 01Jan2014 /Completed  |
| QRS02 | PRN-2001 | SDTM IG v3.2 | 01Jan2018 /Completed |
| QRS03 | PRN-3001 | ADaM IG v1.1 | 01Sep2021/Ongoing  |

 **Additional Content of Interest**

Sponsor clinical group provided reference files ‘aoamicro.xpt’, ‘aogrowth.xpt’ and ‘aostrds.xpt’ spreadsheets used for pooled ADCM, by merging on unique key variables, since this is a multiple record per subject dataset. These are used for ADCM.CMCAT1, CMCAT2, and CMCAT3 category variable derivations. As these datasets do not qualify as ADaM datasets, a Data Definition Table (DDT) is not created in the Define.xml. These datasets in SAS Transport Format Version 5 are placed in “misc” subfolder under Module 5 (m5) of eCTD folder structure (m5 > datasets > ise > misc).

The study QRS03 data was cut-off to perform the Interim Analysis as per the protocol.

##  Traceability Flow Diagram

The following diagram describes the data flow from individual studies to integration.



# Description of Protocols Used in the Integrated Datasets

## Protocol Numbers and Titles

| **Protocol Number** | **Protocol Title / Indication(s)** | **Phase** | **Treatment ARM (s)** | **Treatment ARM(s) not used** |
| --- | --- | --- | --- | --- |
| PRN-1001 | Phase I/II, Multi-Center Clinical Trial to Evaluate Tolerability, Safety and Efficacy of GoodDrug (QRS-MED2022) in Subjects with Advanced Diffuse Large B-Cell Lymphoma (DLBCL) or Mantle Cell Lymphoma (MCL) | II | Trt 1, Trt 2, Trt3 | Not applicable  |
| PRN-2001 | Open label, Phase 2, Randomized study of GoodDrug (QRS-MED2022) Dose 1 vs Dose 2 to Evaluate Safety and Efficacy in Subjects with Advanced Diffuse Large B-Cell Lymphoma (DLBCL)  | II | Trt A, Trt B | Not applicable  |
| PRN-3001 | Phase 3, Randomized Study of GoodDrug vs SOC in Subjects with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) | III | Trt A, Trt B,Trt C  | Not Applicable |

**Additional Content of Interest**

No additional information

## Integrated Analysis Strategy and Design in Relation to Analysis Concepts

The Integration plan defined in the SAP required pooling the efficacy data in ADTR ADRS ADTTE datasets. Integrated ADSL, ADEX and ADEXSUM datasets were created to support subject-level. analyses. Integrated ADCM, and ADQS datasets were created for potential subset or sensitivity analyses.

 ADSL contains the efficacy population flag (EFFFL) to identify all subjects treated with any amount of study drug, GoodDrug (QRS-MED2022), combination or control in their respective study and Intent-To-Treat Population flag (ITTFL) that includes subjects randomized to the study. For integrated analysis, treatment group (TRT01A) is defined as the treatment received if the patient received treatment or the treatment assigned through randomization (TRT01P) if study treatment is not received. A few subjects were randomized but not dosed so their treatment variable (TRT01A) will be blank.

A population flag identifying the Blood Cancer (Lymphoma) subjects was defined as DLBCL. Patient disposition, Demographic and Baseline Characteristics, Pre-Treatment Disease Characteristics, Disease Subtype, Prior Systemic Anti-Cancer Therapy, Radiotherapy and Stem Cell transplant are defined in ADSL for patient summaries. Duration of treatment, total number of cycles dosed, total dose received (in µg and µg/kg), average dose per cycle (in µg and µg/kg) are supported by ADEXSUM.

For QRS01 study, legacy analysis datasets are converted into ADaMv1.1 datasets prior to integrating into the pooled datasets (see legacy conversion plan in Section 8: Appendix, for details). SDTM source data from QRS02 study was used to pool the data per Integrated SAP (see section 5 for additional information on Integrated datasets needed for analyses). Data cutoff date of 01-Sept-2021 was implemented for ongoing study, QRS03 where subjects still are on study drug and has no impact to completed studies-QRS01 and QRS02 due to no additional data after the study DBL.

# Analysis Considerations Related to Integrated Analysis Datasets

## Core Variables

Core variables are those that are represented across all/most integrated analysis datasets.

| **Variable Name** | **Variable Description** |
| --- | --- |
| STUDYID | Study identifier from original study |
| USUBJID | Unique subject identifier from original study |
| SUBJID | Subject identifier from original study |
| SITEID | Site Number from original study |
| REGION1 | Geographic Region1 |
| SITEIDN | Study Site Identifier (N) |
| COUNTRY | Country |
| ARM | Description of Planned Arm |
| ARMCD | Planned Arm Code |
| ACTARM | Description of Actual Arm |
| ACTARMCD | Actual Arm Code |
| AGE | Age |
| AGEU | Age Units |
| AGEGR1 | Pooled Age Group 1 |
| AGEGR1N | Pooled Age Group 1 (N) |
| SEX | Sex |
| SEXN | Sex (N) |
| RACE | Race |
| RACEN | Race (N) |
| RACEGR1 | Pooled Race Group 1 |
| RACEGR1N | Pooled Race Group 1 (N) |
| ETHNIC | Ethnicity |
| ETHNICN | Ethnicity (N) |
| ICFDT | Informed Consent Date |
| ENRLFL | Enrolled Population Flag |
| EFFFL | Efficacy Population Flag |
| FASFL | Full Analysis Set Flag  |
| ITTFL | Intent-To-Treat Population Flag |
| SCRNFCFL | Screen Failure Flag |
| POOL1 | Pooled 1 Population |
| POOL1FL | Pooled Analysis Set 1 Flag |
| POOL2 | Pooled 2 Population |
| POOL2FL | Pooled Analysis Set 2 Flag |
| COMPFL | Completion Status Flag |
|  DLBLCFL | Diffuse Large B-Cell Lymphoma Flag |
| ANCUTDT | Analysis Cut Off date |
| TRT01P | Planned Treatment for Period 01 |
| TRT01PN | Planned Treatment for Period 01 (N) |
| TRT01A | Actual Treatment for Period 01 |
| TRT01AN | Actual Treatment for Period 01 (N) |
| TRT01AG1 | Actual Pooled Trt 1 for Period 01 |
| TRT01AG1N | Actual Pooled Trt 1 for Period 01 (N) |
| TRT01SDT | Date of First Exposure to Treatment 01 |
| TRT01EDT | Date of Last Exposure to Treatment 01 |
| LSTALVDT | Date Last Known Alive |
| ANTISTDT | Subsequent Anti-Cancer Tx Start Date |
| ANTICNFL | Recd Subsequent Anti-Cancer Tx Flag |

## Treatment Variables

ARM versus TRTxxP

Are the values of ARM equivalent in meaning to values of TRTxxP?

 Yes, the meaning is the same, but the ARM values were different across studies, values of

 TRT01P were re-mapped for consistency in the integrated analysis.

|  |  |  |
| --- | --- | --- |
| **STUDYID** | **ARM** | **TRT01P** |
| QRS01  | TRT1 | Active 30 µg/kg  |
| QRS01 | TRT2 | Active 60 µg/kg  |
| QRS01 | TRT3 | Active 90 µg/kg  |
| QRS03, QRS02 | TRTA | Active 60 µg/kg  |
| QRS02 | TRTB | Active 90 µg/kg  |
| QRS03 | TRTC | Placebo |

ACTARM versus TRT01A

If TRTxxA is used, then are the values of ACTARM equivalent in meaning to values of TRTxxA?

Yes, the meaning is same, but the ACTARM values were different across studies, values of

 TRT01A were re-mapped for consistency in the integrated analysis.

|  |  |  |
| --- | --- | --- |
| **STUDYID** | **ACTARM** | **TRT01A** |
| QRS01  | TRT1 | Active 30 µg/kg |
| QRS01 | TRT2 | Active 60 µg/kg  |
| QRS01 | TRT3 | Active 90 µg/kg  |
| QRS03, QRS02 | TRTA | Active 60 µg/kg  |
| QRS02 | TRTB | Active 90 µg/kg  |
| QRS03 | TRTC | Placebo |

Use of Treatment Variables in Integrated Analysis

Are both planned and actual treatment variables used in integrated analysis?

Yes, TRT01A used for Efficacy Analysis and TRT01P used for disposition table(s)

Use of Treatment Grouping Variables in Integrated Analysis

Are both planned and actual treatment grouping variables used in analysis? Yes

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **STUDYID** | **TR01AG1N** | **TR01AG1** | **TR01PG1N** | **TR01PG1** |
|  QRS01, QRS02, QRS03 | 1 | Active <=60 µg/kg  | 1 | Active <=60 µg/kg  |
| QRS01, QRS02 | 2 | Active > 60 µg/kg  | 2  | Active > 60 µg/kg  |

**Additional Content of Interest**

No additional information

## Subject or Protocol Considerations that Require Special Integrated Analysis Rules

Was recoding performed for individual studies to integrate?

Yes

Recoding for study QRS01 included updates to CAT/TESTCD in ADQS to align with CDSIC standard code list and Race variable recoding to CDISC standard rather than CRF coding.

Subject issues that were considered for analysis:

* Subjects QRS02-101-138 and QRS02-502-322 were rescreened. The subjects were randomized in error since they took prohibited medications within the 7 days prior to screening; they were screen failures and were not dosed. These subjects were rescreened 30 days later, were enrolled and given new subject IDs. Their original subject IDs were not included in the total counts of randomized subjects.
* Subjects from site 141 in the QRS02 study were excluded from the integrated efficacy analyses. After database lock of QRS02, observations in study QRS03 led to concerns about data integrity at this site, leading to the exclusion of both safety and efficacy data from this site. For more details, see SAP Section 3.

## Use of Visit Windowing, Unscheduled Visits, and Record Selection

Was windowing used in one or more integrated analysis datasets?

 Yes, visit windowing is used ADQS integrated datasets. Refer to the integrated SAP for more details.

Analysis visit windows were defined in a similar way across studies QRS01, QRS02, and QRS03, with the following differences:

* The EoT analysis visit window ranged up to 10 days after last dose of study drug in QRS01 and up to 7 days after last dose of study drug in QRS03.
* The FU analysis visit window started at 11 days after last dose of study drug in QRS01 and and at 8 days in QRS03.

Because these differences are considered as minor and in order to ensure consistency with the individual study reports, analysis visit windows will not be re-defined in the ISE, but re-used from the individual studies with the following exceptions for study QRS01 and QRS02:

* If a week 4 value is missing, it will be imputed by a non-missing week 2 value.
* If a week 4 and the week 2 value are missing, the week 4 value will be imputed by a non-missing week 1 value (except for diary-based vital sign variables because week 1 values have not been collected).
* The EoT value (7 days post last dose) as derived in study QRS03 will also be used for all studies as the EoT value in the ISS database.

 Were unscheduled visits used in any integrated analysis datasets?

Yes. Both scheduled and unscheduled visits were used in ADQS for assessing consecutive post-baseline visits for Questionnaire (ePRO) data measured at the investigator site.

Were rules used for record selection in one or more integrated analysis datasets?

Yes

ANL01FL was used to define the record selection across all studies for the integrated analysis of Questionnaire (ADQS) datasets. ANL01FL is defined as the assessment closest to the target day when the subject has more than one visit with a measurement within a visit window. In case of ties between observations located on different sides of the target day, the later assessment will be used in the analyses.

**Additional Content of Interest**

No additional information.

## Imputation/Derivation Methods

If date imputation was performed, were there rules that were used in multiple integrated analysis datasets?

Yes.

For ADCM datasets that may contain partial onset or start dates, imputation rules are as follows:

If day is missing and the year and month are the same as the year and month of the first date of study drug dosing, then the date is imputed as the first dosing date. Otherwise, if month and day are missing and year is present, date imputed as the first day of the year. For CM, a missing onset date was imputed according to the conventions mentioned in SAP section 7.5.

No imputation of missing dates for other variables was done.

**Additional Content of Interest**

No additional information.

# Integrated Analysis Data Creation and Processing Issues

## Split Datasets

No datasets needed to be split.

## Data Dependencies

ADSL was used in the creation of all other integrated analysis datasets, mostly for the purpose of deriving subject level variables that were carried into individual datasets. Additionally, ADTTE is derived from ADSL, ADQS and ADTR (see the following table for data dependency information for integrated datasets).

|  |  |
| --- | --- |
| **Dataset Names** | **Data Dependencies** |
| ADCM | ADSL |
| ADEX | ADSL |
| ADEXSUM | ADSL, ADEX |
| ADQS | ADSL |
| ADTR | ADSL |
| ADRS | ADSL |
| ADTTE | ADSL, ADQS, ADTR |

## Intermediate Datasets

No intermediate datasets created.

**Additional Content of Interest**

No additional information

# Integrated Analysis Datasets Descriptions

## Overview

Is an integrated statistical analysis plan included in the submission?

Yes, see the analysis plan document: “QRS-MED2022 Integrated Efficacy Statistical Analysis Plan”.

Do the integrated datasets support all statistical analysis plan specified objectives?

Yes. The integrated ADaM datasets support the integrated analysis Statistical Analysis Plan (SAP) specified objectives.

**Additional Content of Interest**

No additional information

## Integrated Analysis Datasets

| **Dataset NameDataset Label** | **Class** | **Efficacy(E)/****Immunogenicity(I)/Safety(S)** | **Baseline or other subject characteristics** | **All studies contribute** | **Structure** |
| --- | --- | --- | --- | --- | --- |
| [ADSL](#_5.2.1_ADSL_–)Subject Level Analysis Dataset | ADSL |  | X | X | One observation per subject |
| [ADCM](#_5.2.2_ADCM_–)Concomitant Medications Analysis Dataset | OCCDS | S | X |  | One record per medication per subject  |
| [ADEX](#_5.2.3_ADEX_–) Exposure Analysis Dataset | ADAM OTHER | S |  | X | One record of drug exposure, per instance or duration per subject  |
| [ADEXSUM](#_5.2.4_ADEXSUM_–) Exposure Summary Analysis Dataset | BDS | S |  | X | One record per subject per exposure parameter  |
| [ADQS](#_5.2.5_ADQS_–)Questionnaires Analysis Dataset | OCCDS | E |  | X | One record per questionnaire result per visit per subject  |
| [ADTR](#_5.2.6_ADTR_–)Tumor MeasurementAnalysis Dataset |  BDS | E |  | X | One record per tumor measurement parameter per derivation type per visit per subject |
| [ADRS](#_5.2.7_ADRS_–) Overall Response  Analysis Dataset | BDS | E |  | X | One record per response parameter per subject  |
| [ADTTE](#_5.2.8_ADTTE_–) Time to Events Analysis Dataset | BDS | E |  | X | One record per analysis parameter per subject  |

### 5.2.1 ADSL – Subject-Level Analysis Dataset

ADSL has the subject-level information that includes all subjects to be analyzed in the integrated datasets.

For QRS01 study, Subject IDs from legacy analysis data are in non-standard format, so subjects 001100, 001362, and 002134 are re-mapped to USUBJID: QRS01-001-100, QRS01-001-362 and QRS01-002-134 respectively for data integration, refer to Appendix 8: Legacy Data Conversion Plan (LDCP) for additional information. SDTM data from QRS02 study is transformed using ADaM IG v1.1 standard for integration purposes. Data snapshot with cut-off date: 01SEP2021 used for integration of QRS03.ADSL dataset as the study is still on-going.

ADSL includes required ADaM variables for demographics, subject characteristics, baseline disease characteristics, disposition, treatment assignment and population flags, see section 3.1 for list of core variables. Also, it contains other subject-level variables, including key information corresponding to conduct of study and critical variables used in analyses as follows-

 Death related variables:

 DTHDT (Date of Death)

 DTHFL (Subject Death Flag)

 DTH2FL (Death within 30 days of Last Dose Flag)

Subgroup variables:

AGEGR1: Age group (<55, ≥55 - < 65, ≥ 65 - < 75, ≥ 75 years). In summary tables, the grouping is <65 years vs ≥ 65 years (includes ‘>=65 - <75 year’ and ‘≥ 75 years’)

SEX: Sex (Male, Female)

RACEGR1: Race (WHITE, BLACK and OTHER). In summary tables, the grouping is White vs Black vs All Others (includes ‘Others’ and missing)

COUNTRY: Country code (BEL, CHE, ESP, FRA, GBR, ITA and USA). In summary table, regions are grouped into USA and Europe (including country of BEL, CHE, ESP, FRA, GBR and ITA).

Flag variables:

 DLBCLFL: Diffuse Large B-Cell Lymphoma Flag (Y/N)

See section 3.1 for the list of core variables that are carried into all other analysis datasets. In addition, other variables used in subgrouping summaries include demographic grouping variables for age and years since disease onset.

The population variables EFFFL and ITTFL were not included in ADSL dataset for

ISE; instead, they were replaced with variables EFFISE and ITTISE.

• EFFISE (Integrated Efficacy Population Flag): This variable identifies subjects in

the Efficacy (ISE) population. It takes a value of ‘Y’ if the subject was in study

QRS01 and received at least one dose of study drug (QRS-MED2022).

In QRS02, subjects received at least dose of either of the study drug doses. For QRS03, subjects received at least one dose of study drug or standard of care medication. Otherwise, it takes a value of ‘N’ if that criterion is not met. This population flag was used for efficacy related summaries.

• ITTISE (Integrated Intent-to-Treat Population Flag): This variable identifies

subjects in the ITT population. It takes a value of ‘Y’ if the subject was

randomized to any of the three studies QRS01, QRS02 and QRS03. Otherwise, ITT population flag is assigned a value of ‘N’. This population flag was used for efficacy related summaries.

In study QRS01, three subjects (QRS01-001-100, QRS01-001-362 and QRS01-002-134) were randomized but did not receive any study treatment. For these subjects, ITTISE was assigned as ‘Y’, EFFISE was assigned as ‘N’, and TRT01A/TRT01AN (actual treatment) were set to missing since no treatment was received.

Also, in study QRS02, two subjects were enrolled but did not receive study treatment. Subject QRS02-101-138 and QRS02-502-322 were randomized in error, and Subject QRS02-502-242 withdrew consent to pursue holistic therapy. For these two subjects, both EFFISE and ITTISE were assigned as ‘N’, and TRT01A/TRT01AN were set to missing since no treatment was received.

### 5.2.2 ADCM – Concomitant Medications Analysis Dataset

This dataset was created for the purpose of creating all tables and listings for

concomitant medication, anti-cancer therapy, blood product/blood supportive care product, steroid use, and antimicrobial use analysis. Pooled ADCM used reference files ‘aoamicro.xpt’, ‘aogrowth.xpt’ and ‘aostrds.xpt’, by merging on unique key variables, since this is a multiple record per subject dataset. For study QRS02, not all SUPPCM records were merged back to ADCM, but only the records needed for derivation of customized categories, steroid

and antimicrobial flags.

ADCM dataset contains data from three different source studies: QRS01, QRS02, and QRS03. The concomitant medications are coded with WHO-DICT. For studies QRS03 and QRS02 the WHO-DD version is: MAR2019, and for study QRS01, the WHO-DD version is: MAR2014.

No re-coding was performed because prior and concomitant medications were used in limited analyses.

### 5.2.3 ADEX – Exposure Analysis Dataset

ADEX contains study drug administration and is one record per subject per administration from SDTM EX domain where planned dose, dose prepared, concentration or dilution and infusion status of complete or partial infusion at each cycle were carried over. Variables for actual dose in µg and weight adjusted actual dose in µg/kg were derived at each administration. All 3 studies are included in the submitted Integrated database to support analyses in each pooling group.

### 5.2.4 ADEXSUM – Exposure Summary History Analysis Dataset

This dataset is derived from ADEX at one record per subject per derived analysis parameter and provides drug exposure summary information. PARAM for PARAMCD of NCYCTOT, DOSDURD, DOSTOT, MDOSTOT are listed in table below.

| **PARAMN** | **PARAMCD** | **PARAM** | **AVAL** |
| --- | --- | --- | --- |
| 1 | NCYCTOT | Total Number of Cycles Dose Administered | Count of unique number of ADEX.VISITNUM where study drug (ADOSE is not missing) is administered per subject. Cycle number is the second string in EX.VISIT (e.g. CYCLE 1 DAY 1). |
| 2 | DOSDURD | Duration of Treatment (days) | ADSL.TRTDURD (Duration of exposure = date of last exposure – date of first exposure +1). |
| 3 | DOSTOT | Total Actual Dose Taken (µg) | Sum up actual dose administered, ADEX.ADOSE over all cycles where study drug is administered per subject. |
| 4 | MDOSTOT | Average of Total Actual Dose Per Cycle (µg) | It will be the average of Total Actual Dose Taken (µg) (DOSTOT) / Total Number of Cycles dosed (NCYCTOT) where study drug is administered. |

### 5.2.5 ADQS – Questionnaire Analysis Dataset

This dataset was created for the purpose of creating all tables and listings relating to ECOG performance status, PRO scores based on cancer health related quality of life questionnaires (see below) used to calculate proportion of patients with improvement/deterioration.

* European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-Core 30 (C30),
* Lymphoma subscale (LymS) of Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym),
* EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L).

Legacy datasets QUEST1, QUEST2, QUEST3 from QRS01 study that are based on QOL questionnaires, transformed into ADaM IGv1.1 standard for integration purposes, see Appendix 8 for more information on the Legacy Data Conversion Plan. For QRS02 study, ADQS was produced from SDTM CE, QS domains, supplemental qualifier SUPPSU, and ADSL by merging on unique key variables, since this is a multiple record per subject dataset.

In addition to the original records carried from SDTM QS domain, additional records

were created to capture the worst-case post baseline and best-case post baseline for

parameter ‘ECOG1-Performance Status’.

• Worst-Case Post Baseline: Variable AVAL was populated with the highest post

baseline value for each subject, variable AVISIT was set to ‘Worst-Case Post

Baseline’, and DTYPE was set to ‘WC’.

• Best-Case Post Baseline: Variable AVAL was populated with the lowest post

baseline value for each subject, variable AVISIT was set to ‘Best-Case Post

Baseline’, and DTYPE was set to ‘BC’.

Note that both scheduled and unscheduled visit records were used in determination of the

worst-case and best-case post baseline.

See table below listing the DTYPE, derivation rule and any controlled terminology used.

| **ADaM Dataset**  | **Derivation Rule**  | **Controlled Terminology**  |
| --- | --- | --- |
| ADQS.DTYPE | QRS01.ADQS.DTYPE: Derived from QUEST1/QUEST2/QUEST3 legacy datasets (see below for Appendix 8: Legacy conversion plan). QRS02.ADQS.DTYPE: Derived from SDTM QS test codes, assign ‘WC’ for the highest post baseline value for each subject; else 'BC' for lowest post baseline value for each subject. QRS03.ADQS.DTYPE replacing the value 'MAXIMUM' by ‘WC' when AVISITN=7777; ‘MINIMUM’ by ‘BC’ when AVISITN=5555 |  WC, BC |

### 5.2.6 ADTR – Tumor Measurement Analysis Dataset

This dataset was created for the purpose of creating all tables relating to organ examination.

For QRS02 study, SDTM TR domain and ADSL by merging on unique key variables since this is a multiple record per subject dataset and legacy datasets for data integration. ADTR dataset from QRS03 study and legacy datasets BLTTEST, TRESULT from QRS01 study that are transformed per LDAP (see Appendix 8), used to produce integrated ADTR.

Only the spleen and liver assessment by physical examination at the scheduled visits

were carried to this dataset for summary.

### 5.2.7 ADRS – Response Analysis Dataset

This dataset was created for the purpose of creating tables and listings relating to overall response. Integrated ADRS was produced from SDTM RS domain from study QRS02, and ADRS datasets from studies QRS01 and QRS03.

In ADRS, there are four parameters. Two of them (PARAMCD = OVRESP or BESTRESP)

carried the investigator-assessed response data directly from SDTM RS domain from study QRS02, and ADRS datasets from studies QRS01 and QRS03. The other two parameters (PARAMCD = OVRESP1P or OVRESP1P) were derived for analysis need.

Visit-level response (PARAMCD=OVRESP): This parameter captured the investigator-assessed response at each visit for both studies QRS02 and QRS03. Note that visit-level response wasn’t collected in study QRS01.

Best response (PARAMCD=BESTRESP): This parameter captured the investigator assessed

best (or overall) response.

o For study QRS01, the overall response was assessed by the

investigator at Cycle 4 Day 1, one-month follow-up, and 3-month follow-up.

o For study QRS02, the overall response was assessed by the

investigator at the protocol-defined time points of ‘after 3 cycles’, ‘after 6

cycles’, and ‘after the last dose, if not after 6 cycles’.

o For study QRS03, the best overall response across study visits was

provided by the investigator (data cut-off: 01Sep2021).

**Parameters created for analysis need:**

Overall response after last dose (PARAMCD=OVRESP1P): This parameter was

derived for the analysis of Overall Response Rate (ORR).

o For study QRS01, overall response after last dose was set to the

overall response assessed by the investigator at the visit for 3-month

follow-up.

o For study QRS02, overall response after last dose was

programmatically derived by the sponsor based on the investigator assessed

overall response at three protocol-defined time points. The

overall response at the time point 'after 6 cycles' was used if it existed;

otherwise, the overall response at the time point 'after the last dose, if not

after 6 cycles' was used. If the overall response was not available at both

'after 6 cycles' and 'after the last dose, if not after 6 cycles', then the overall

response at the time point 'after 3 cycles' was used.

o For study QRS03, overall response after last dose was set to the best

overall response provided by the investigator (data cut-off: 01Sep2021).

Programming-derived investigator-assessed overall response (PARAMCD=OVRESP2P): This parameter was created for the analysis of ORR based on the visit-level response as originally specified in the Integrated SAP. However, the derivation algorithm for ORR was later modified based on the overall response assessed by the investigator at protocol-defined time points (see above description under ‘OVRESP1P’). As a result, this parameter was no longer required for the analysis but still retained in the ADRS dataset.

The ISE tables of investigator-assessed objective overall response rate and related subgroup analyses were based on the parameter OVRESP1P. The other parameter OVRESP2P was not used in any of the integrated efficacy analyses. Note that in studies QRS02 and QRS03, primary efficacy analyses will be based on CRR according to the 2014 Lugano classification (Cheson et al., 2014) as determined by the investigator in all DLBCL patients that received study drug (QRS-MED2022) at each visit cycle.

### 5.2.8 ADTTE – Time to Event Analysis Dataset

This dataset was created for the purpose of creating all time-to-event related

tables, listings, and figures. Integrated ADTTE was produced from SDTM CE, CM, QS, SV domains from QRS02 study, ADQS, ADTR and ADSL datasets from QRS01 and QRS03 studies.

Only investigator-assessed response was included in the efficacy analyses, and only those from studies QRS02 and QRS03 were used in the ISE tables and figures, see ISE SAP.

ADTTE dataset was used to compute key efficacy endpoints, see below.

* Complete Response Rate (CRR)
* Overall Response Rate (ORR)
* Disease Control Rate (DCR)
* Duration of Response (DOR)
* Relapse-Free Survival (RFS)
* Progression Free Survival (PFS)
* Overall Survival (OS)

Note that the parameters DOR, CRR and ORR were derived for responders only, where ‘responders’ consisted of subjects who reached a response better than stable disease. DCR was derived for subjects who reached a response of stable disease or better. All other parameters were derived for all subjects in the ITTISE population.

# Data Conformance Summary

## Conformance Inputs

Specify the software name and version used for the integrated datasets validation

 Pinnacle 21 Enterprise v4.1.4, Validation Engine version 1907.2

Specify the version of the validation rules (i.e. CDISC, FDA, PMDA) for the integrated datasets

Used ADaM IG version 1.1 individual study validation rules for FDA as there are no validation rules available for integrated studies.

Specify the software name and version for the define.xml validation

Pinnacle 21 Enterprise v 4.1.4, Define-XML v2.0

Specify the version of the validation rules (i.e. CDISC, FDA, PMDA) for the define.xml

 ADaM IG version 1.1 for FDA

Provide any additional compliance evaluation information:

 Not Applicable

## Issues Summary

The following table summarizes the issues found by the conformance validation:

| **Dataset** | **Rule ID** | **Diagnostic Message** | **Severity** | **Count** | **Explanation** |
| --- | --- | --- | --- | --- | --- |
| ADSL | AD1016 | Secondary variable BRTHDTC is populated but its primary variable BRTHDT is not populated  | Error | 24 | BRTHDTC has partial dates on fourteen records which were not imputed per individual study protocol/SAP |
| ADSL | CT2012 | RACE value not found in 'Race' extensible codelist | Warning  | 101 | RACE is a non-extensible codelist. However, RACE=OTHER is populated if race was collected via ‘Other, Specify’ field in the CRF. As per CDISC/ SDTMIG v3.2, Section 5 Models for Special-Purpose Domains, Demographics (DM); if the race was collected via an ‘Other, Specify’ field and the sponsor chooses not to map the value then the value of RACE should be ‘OTHER’. |
| ADEX | CT2012 | RACE value not found in 'Race' extensible codelist | Warning  | 105 | RACE is a non-extensible codelist. However, RACE=OTHER is populated if race was collected via ‘Other, Specify’ field in the CRF. As per CDISC/ SDTMIG v3.2, Section 5 Models for Special-Purpose Domains, Demographics (DM); if the race was collected via an ‘Other, Specify’ field and the sponsor chooses not to map the value then the value of RACE should be ‘OTHER’. |
| ADEX | AD1017 | Secondary custom variable is present but its primary variable is not present | Warning | 7 | DELAYRSN/PRTLRSN/INTRSN/EXDOSPLN are primary variables in the dataset. Consulted P21 and is a false positive message produced by Pinnacle 21 Enterprise system |
| ADEXSUM | CT2012 | RACE value not found in 'Race' extensible codelist | Warning  | 24 | RACE is a non extensible codelist. However, RACE=OTHER is populated if race was collected via ‘Other, Specify’ field in the CRF. As per CDISC/ SDTMIG v3.2, Section 5 Models for Special-Purpose Domains, Demographics (DM); if the race was collected via an ‘Other, Specify’ field and the sponsor chooses not to map the value then the value of RACE should be ‘OTHER’. |
| GLOBAL | AD1034 | Traceability rules not executed due to missing DM dataset | Error | 1 | For study QRS01 source data is in legacy format, converted to ADaM IG v1.1. Hence, no SDTM data is available.  |
| GLOBAL | AD1036 | Traceability rules not executed due to missing EX dataset | Error | 1 | For study QRS01 source data is in legacy format, converted to ADaM IG v1.1. Hence, no SDTM data is available. |

# Submission of Programs

All programs for the integration of analysis datasets and key efficacy results are submitted. They were all created on a Linux platform using SAS v9.4. The internal reference date used to create dates in integrated ADaM datasets is 01 January 1960.

## Integrated ADaM Programs

| **Program Name** | **Output** | **Macro Used** |
| --- | --- | --- |
| ADSL.txt | ADSL.xpt |  |
| ADCM.txt | ADCM.xpt |  |
| ADEX.txt | ADEX.xpt |  |
| ADEXSUM.txt | ADEXSUM.xpt |  |
| ADQS.txt | ADQS.xpt | viswin.txt |
| ADRS.txt | ADRS.xpt |  |
| ADTR.txt | ADTR.xpt |  |
| ADTTE.txt | ADTTE.xpt |  |
|  |  |  |

## Integrated Analysis Output Programs

| **Program****Name** | **Output****Number** | **Title** | **Input** |
| --- | --- | --- | --- |
| T\_14\_2\_1\_eff | 14.2.1 | Summary of Efficacy | ADSL, ADTTE |
| <program names> |  |  |  |

## Macro Programs

| **Program****Name** | **Purpose** |
| --- | --- |
| viswin.txt | Visit Windows creation for record selection |
| Sumn.txt | Counts of subjects per population |

# Appendix

|  |
| --- |
| Legacy Data Conversion Plan and Report Appendix |

# Purpose

The purpose of this appendix is to document the traceability of legacy data when this was done within the integration.

Because of transformations required during this conversion, some of the terms, categories and data formats used in the data have been translated into CDISC standard formats. This appendix identifies differences between the legacy data and integrated data and explains how the integrated data represents the equivalent data.

# Conversion Data Flow

The legacy data was converted to ADaM data flow diagram. See Section 1.5 for the complete integration flow diagram.



**Rationale:**

Legacy analysis data was converted to ADaM datasets for study QRS01 for use in the Integrated Summary of Efficacy .

# Converted Data Summary

The study QRS01 started before December 17, 2016. Therefore, standard data is not required. The legacy tabulation data was used to create legacy analysis data, which was used for creating analysis results for the appendix of the CSR.

For this submission,

• Legacy analysis data was converted to ADaM to facilitate ISE ADaM integration.

During authoring of the mapping specification from legacy data to ADaM, CDISC Controlled Terminology was applied where applicable. After authoring of a mapping specification and programming of the ADaM SAS datasets, the Pinnacle21 validator was run to check compliance to ADaM IG 1.1. Checks that signified a programming issue were addressed and the relevant ADaM datasets were updated when possible.

|  |  |  |  |
| --- | --- | --- | --- |
| **Study ID** | **Legacy Dataset Names** | **Legacy Dataset Description** | **Mapped To ADaM Dataset** |
| QRS01 | DEMOG, MEDHX, VITALS, CMED, DEATH | Demographics, Medical History, Vital Signs, Concomitant Medications, Death details | ADSL |
|  | CMED, PRIORMED | Concomitant Medications, Prior Medications | ADCM |
|  | DRUGADM, DOSECOMPL | Drug Administration, Dose Compliance | ADEX |
|  | QUEST1, QUEST2, QUEST3 | Questionnaire 1 (EORTC-QLQ-C30), Questionnaire 2 (FACT-Lym), Questionnaire 3 (EQ-5D-5L) | ADQS |
|  | BLTTEST, TRESULT | Baseline Tumor Measurements, Tumor Measurement Results | ADTR |
|  | TRESPONSE | Tumor Response  | ADRS |

## Issues Encountered and Resolved

A comparison between newly created key ADaM datasets and their corresponding legacy analysis data and CSR analysis results was completed to ensure traceability. See below for a description of issues encountered and their resolutions:

• Creation of ADSL was based on the legacy analysis dataset DEMOG. This legacy file contained all demographics, disposition and population flags. We have followed ADaM model v2.1 and ADaMIG v1.1 to create ADSL based on the legacy analysis data. Here is a summary of the variable changes:

o The original population flags were numeric. The numeric values were converted from 1 to Y

and 0 to N.

o The define show how variables were renamed from the legacy data to the correct ADaMIG

v1.1 variables.

* The ITT (intent-to-treat) population flag did not exist in the legacy analysis data. The flag was

derived in the ADaM programs for the subjects who are randomized.

o Originally phases were referred to as periods in the legacy analysis data but in order to be

ADaM compliant the following changes were made:

▪ Baseline Phase is PH1SDT and PH1EDT

▪ Treatment Phase is PH2SDT and PH2EDT. This phase contains Up-titration (APERIOD = 1, AP01SDT, AP01EDT), Maintenance (APERIOD=2, AP02SDT, AP02EDT), and Down-titration (APERIOD= 3, AP03SDT, AP03EDT) periods.

▪ Safety Follow-up Phase is PH3SDT and PH3EDT.

O Discontinuation Reason (DCSREAS) is mapped from the original values to CDISC controlled terminology as follows:

|  **Legacy Analysis****Data Value** | **CSR Reported****Value** | **ADSL.DCSREAS** |
| --- | --- | --- |
| termination due to other reasons | Other | OTHER |
| termination due to unsatisfactory compliance of subject | Non-Compliance | NON- COMPLIANCE WITH STUDY DRUG |
| termination because subject withdrew consent | Subject WithdrewConsent | WITHDRAWAL BY SUBJECT |
| termination with major protocol violation per investigator | Physician Discontinued Subject Due to Protocol Violation | PROTOCOL DEVIATION |
| termination with lack of efficacy | Lack of Efficacy | LACK OF EFFICACY |
| termination due to adverse event | Adverse Event | ADVERSE EVENT |
| lost to follow up, reason for termination unknown | Lost to Follow-Up | LOST TO FOLLOW-UP |

• The source dataset TRESPONSE was not in the BDS structure. This was changed with the creation of ADRS and the variable names OVRESP and BOVRESP became PARAMCD = OVRESP and PARAMCD = BESTRESP, respectively and then unique one-to-one matches were created for PARAM. Please see the define.xml for the full list. Then BASE, CHG, and PCHG were created along with ANLxxFL and CRITyFLs were created.

• The legacy questionnaire datasets were already in a similar structure to BDS but the variables were changed to be ADaM IG v1.1 compliant where necessary. The define.xml has the code lists for PARAM and PARAMCD.

• Within ADCM the coding from the legacy dataset have been remapped to the WHO Drug coding variables from the OCCDS v1.0. ATC code variables were derived in ADaM ADCM using CMTERM from the legacy analysis data as per WHODD Version Global B3 Mar2019. Also, only ANTI-CANCER THERAPY data is retained for creating ADCM for the integration purpose. Partial start and end dates were populated as is in ADaM ADCM with no imputation.

# Outstanding Issues

No outstanding issues to report.