

Integrated Analysis Data Reviewer's Guide

QRS Pharmaceuticals

QRS-MED2022

Integrated Summary of Efficacy

iADRG Version 1.0

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Integrated Analysis Data Reviewer's Guide

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1. Introduction

1.1 Purpose

This document provides context for the integrated analysis datasets and terminology that benefit from additional explanation beyond the Data Definitions document (Define-XML) for integrated studies and a summary of integrated analysis data conformance findings. This also includes details regarding any legacy data conversion that was done within the integration.

1.2 Acronyms

Acronym	Definition
iADRG	Integrated Analysis Data Reviewer's Guide
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
MCL	Mantle Cell Lymphoma
MTD	Maximum Tolerated Dose
NA	Not Applicable
RDE	Recommended Dose for Expansion
NCI	National Cancer Institute
SCE	Summary of Clinical Efficacy
SMQ	Standardized MedDRA Query
SOC	Standard-of-Care
TAUG	Therapeutic Area User Guide

1.3 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 1.1 OCCDS v1.0 ADaM Basic Data Structure for Time-to-Event Analyses v1.0
ADaM Controlled Terminology	ADaM CT 2020-11-06
Data Definitions	Define-XML v2.0
TAUG	Not Applicable
Medications Dictionary	WHODD Version Global B3 Mar2019
Medical Events Dictionary	MedDRA v23.1 (includes COVID-19 terminology)
Other Standards	CTCAE v5.0

Additional Content of Interest

No additional information.

1.4 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 2.1/IG 1.1)	01Jan2014/Completed
QRS02	PRN-2001	SDTM 1.4/IG 3.2	01Jan2018/Completed
QRS03	PRN-3001	ADaM 2.1/IG 1.1	01Sept2021/Ongoing

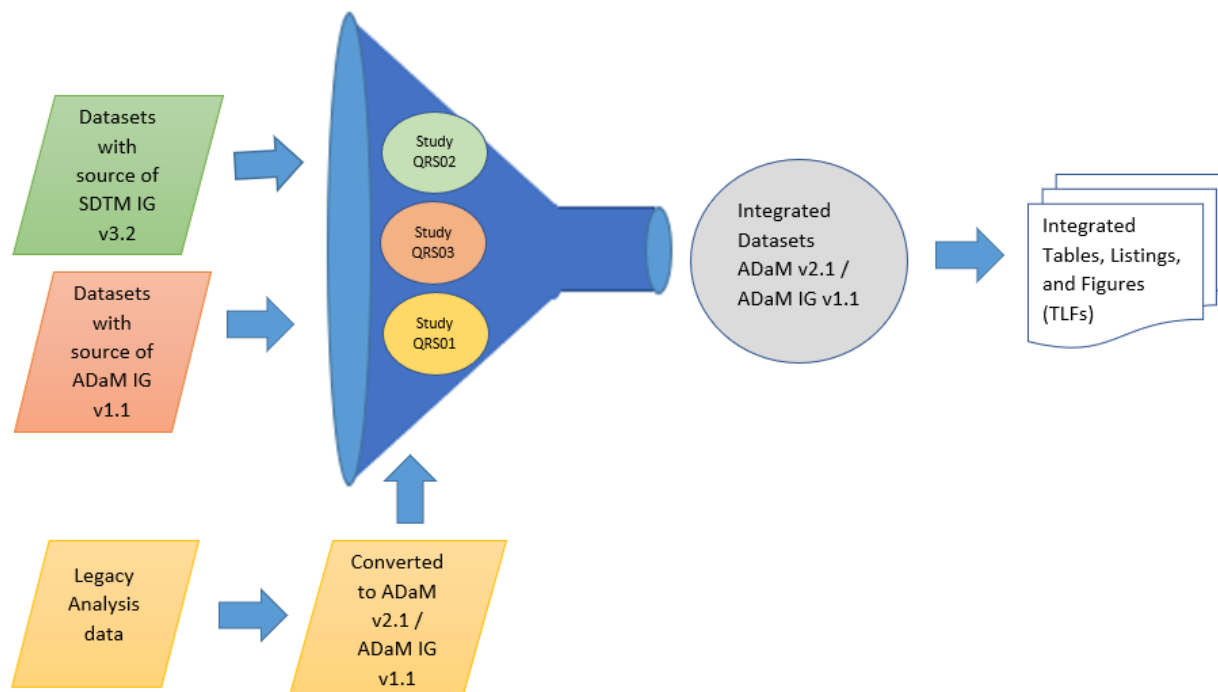
Additional Content of Interest

The sponsor clinical group provided reference data files 'aoamicro.xpt', 'aogrowth.xpt' and 'aostrds.xpt' 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 Define-XML. These datasets in SAS Version 5 Transport Format are placed in the "misc" subfolder under Module 5 (m5) of the eCTD folder structure (m5 > datasets > misc).

The study QRS03 data was pooled into integration from individual study Interim Analysis 3 data with cutoff-date 01Sept2021.

1.5 Traceability Flow Diagram

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



2. Description of Protocols Used in the Integrated Datasets

2.1 Protocol Numbers and Titles

Protocol Number	Indication(s)/Protocol Title	Phase	Treatment ARM(s)
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, Trt 3
PRN-2001	Open-Label, Phase II Randomized Study of GoodDrug (QRS-MED2022) Dose 1 vs	II	Trt A, Trt B

Protocol Number	Indication(s)/Protocol Title	Phase	Treatment ARM(s)
	Dose 2 to Evaluate Safety and Efficacy in Subjects with Advanced Diffuse Large B-Cell Lymphoma (DLBCL)		
PRN-3001	Phase III 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

Additional Content of Interest

No additional information.

2.2 Integrated Analysis Strategy and Design in Relation to ADaM Concepts

The integration strategy defined in the statistical analysis plan (SAP) required pooling the efficacy data in ADTR, ADRS and ADTTE datasets. Integrated ADSL, ADEX and ADEXSUM datasets were created to support subject-level analyses. Integrated ADCM, and ADQS, datasets were created for potential subsets 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 from their respective study. The intent-to-treat population flag (ITTFL) includes subjects randomized to the study. For integrated analysis, actual treatment group (TRT01A) is defined as the treatment that the patient received. Planned treatment is defined as the treatment assigned to the patient through randomization (TRT01P). A few subjects were randomized but not dosed, so their actual treatment variable (TRT01A) is blank.

A population flag identifying the Blood Cancer (Lymphoma) subjects was defined as DLBCLFL. Patient Disposition, Demographic and Baseline Characteristics, 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) and average dose per cycle (in µg and µg/kg) are supported by ADEXSUM.

For study QRS01, legacy analysis datasets are converted into ADaM v1.1 datasets prior to integrating into the pooled datasets. (See the Legacy Data Conversion Plan and Report Appendix in section 8 for details.) SDTM source data from study QRS02 was used to pool the data per the integrated SAP. (See section 5 for additional information on integrated datasets needed for analyses.) The data cutoff-date of 01Sept2021 was implemented for ongoing study QRS03, where subjects are still on the study drug; this has no impact on completed studies QRS01 and QRS02 as there will be no changes to the data after the study DBL.

3. Analysis Considerations Related to Integrated Analysis Datasets

3.1 Core Variables

Core variables are those that are represented across all 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 Region 1
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

Variable Name	Variable Description
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
COMPLFL	Completers Population Flag
DLBCLFL	Diffuse Large B-Cell Lymphoma Flag
ANCUTDT	Analysis Cutoff Date
TRT01P	Planned Treatment for Period 01
TRT01PN	Planned Treatment for Period 01 (N)
TRT01A	Actual Treatment for Period 01

Variable Name	Variable Description
TRT01AN	Actual Treatment for Period 01 (N)
TRT01AG1	Actual Pooled Treatment 1 for Period 01
TRT01AG1N	Actual Pooled Treatment 1 for Period 01 (N)
TR01SDT	Date of First Exposure to Treatment in Period 01
TR01EDT	Date of Last Exposure to Treatment in Period 01
LSTALVDT	Date Last Known Alive
ANTISTDT	Subsequent Anti-Cancer Therapy Start Date
ANTICNFL	Subsequent Anti-Cancer Therapy Flag

3.2 Treatment Variables

ARM versus TRTxxP

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

Yes, the meaning is the same, but the ARM values were different across studies: the values of TRT01P were remapped 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 the values of TRTxxA?

Yes, the meaning is same, but the ACTARM values were different across studies: the values of TRT01A were remapped 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 is used for efficacy analysis and TRT01P is used for disposition table(s).

Use of Treatment Grouping Variables in Integrated Analysis

Are both planned and actual treatment grouping variables used in integrated 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.

3.3 Subject or Protocol Considerations that Require Special Integrated Analysis Rules

Were any additional updates (e.g., codelists, value-level metadata, dictionaries) performed when integrating?

Yes.

- Recoding was done for study QRS02 from SDTM data to ADaM to create PARAMCDs from TESTCD variables to generate ADQS.

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, 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 study QRS02 were excluded from the integrated efficacy analyses. After database lock, observations 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.

Additional Content of Interest

No additional information.

3.4 Use of Visit Windowing, Unscheduled Visits and Record Selection

Was windowing used in one or more integrated analysis datasets?

Yes. Visit windowing was used in ADQS integrated dataset. 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 at 8 days in QRS03.

Because these differences are considered minor and to ensure consistency with the individual study reports, analysis visit windows will not be redefined in the ISE, but re-used from the individual studies with the following exceptions for studies 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 a week 2 value are missing, the week 4 value will be imputed by a non-missing week 1 value.
- 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 ISE database.

Were unscheduled visits included 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 the 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 to document.

3.5 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 the day is missing and the year and month are the same as the year and month of the first date of the study drug dosing, then the date is imputed as the first dosing date. Otherwise, if month and day are missing and year is present, the date is 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.

4. Integrated Analysis Data Creation and Processing Issues

4.1 Split Datasets

No datasets needed to be split.

4.2 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, ADEXSUM is derived from ADEX and ADTTE is derived from ADQS and ADTR. (See the following table for data dependency information for integrated datasets.)

The sponsor clinical group provided reference data files 'aoamicro.xpt', 'aogrowth.xpt' and 'aostrds.xpt' were used for pooled ADCM. Refer to section 1.4 for further information.

Dataset Name	Data Dependencies
ADCM	ADSL, AOAMICRO, AOGROWTH and AOSTRDS
ADEX	ADSL
ADEXSUM	ADSL, ADEX
ADQS	ADSL
ADRS	ADSL
ADTR	ADSL
ADTTE	ADSL, ADQS, ADTR

4.3 Intermediate Datasets

No intermediate datasets created.

Additional Content of Interest

No additional information.

5. Integrated Analysis Dataset Descriptions

5.1 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 integrated statistical analysis plan specified objectives?

Yes. The integrated ADaM datasets support the integrated analysis statistical analysis plan specified objectives.

Additional Content of Interest

No additional information.

5.2 Integrated Analysis Datasets

Dataset Name Dataset Label	Class	Efficacy (E)/ Safety (S)/ Immunogenicity (I)	Baseline or Other Subject Characteristics	All Studies Contribute	Structure
<u>ADSL</u> Subject-Level Analysis Dataset	ADSL		X	X	One record per subject
<u>ADCM</u> Concomitant Medications Analysis Dataset	OCCDS	S	X	X	One record per medication per subject
<u>ADEX</u> Exposure Analysis Dataset	ADaM OTHER	S		X	One record of drug exposure, per instance or duration per subject

Dataset Name Dataset Label	Class	Efficacy (E)/ Safety (S)/ Immunogenicity (I)	Baseline or Other Subject Characteristics	All Studies Contribute	Structure
<u>ADEXSUM</u> Exposure Summary Analysis Dataset	BDS	S		X	One record per subject per exposure parameter
<u>ADQS</u> Questionnaire Analysis Dataset	BDS	E		X	One record per questionnaire result per visit per subject
<u>ADRS</u> Overall Response Analysis Dataset	BDS	E		X	One record per response parameter per subject
<u>ADTR</u> Tumor Measurement Analysis Dataset	BDS	E		X	One record per tumor measurement parameter per derivation type per visit per subject
<u>ADTTE</u> 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 subject-level information that includes all subjects to be analyzed in the integrated datasets. Study QRS01 has legacy data in non-standard format; refer to section 8, Legacy Data Conversion Plan and Report Appendix, for additional information. SDTM data from study QRS02 was transformed using the ADaM IG v1.1 standard for integration purposes. Data snapshot with cutoff-date 01SEP2021 was used for integration of the QRS03.ADSL dataset as the study was still ongoing.

ADSL includes required ADaM variables for demographics, subject characteristics, baseline disease characteristics, disposition, treatment assignment and population flags. See section 3.1 for the list of core variables. Also, it contains other subject-level variables, including key information corresponding to the conduct of the 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 tables, regions are grouped into USA and Europe (including countries 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. Two levels of pooling are used in integrated datasets as per pooling flag variables POOL1FL and POOL2FL that are included in ADSL. All DLBCL patients receiving at least one dose of the study drug are considered for POOL1 summary tables. All subjects receiving at least one dose of the study drug from any of the clinical protocols, regardless of the disease condition, are included in the POOL2 table summaries.

The population flag variables EFFF and ITTFL are from individual studies. In the integrated ADSL dataset, population flag variables EFFISEFL and ITTISEFL were created.

- EFFISEFL (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 the study drug (QRS-MED2022). In QRS02, subjects received at least one dose of either of the study drug doses. For QRS03, subjects received at least one dose of the 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.

- **ITTISEFL (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, the 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, ITTISEFL was assigned as 'Y', EFFISEFL 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. Subjects 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 EFFISEFL and ITTISEFL 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 products/blood supportive care products, 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. The 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 recoding 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 the 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 three 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 the 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 the 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 and 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 study QRS01 that are based on QOL questionnaires are transformed into the ADaM IG v1.1 standard for integration purposes. See section 8 for more information on the Legacy Data Conversion Plan and Report Appendix. For study QRS02, ADQS was produced from SDTM CE, QS domains, supplemental qualifier SUPPQS 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 the 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 PostBaseline' 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 PostBaseline' 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 the table below listing the DTYPE, derivation rule and any controlled terminology used.

ADaM Variable	Derivation Rule	Controlled Terminology
ADQS.DTYPE	<p>QRS01.ADQS.DTYPE: Derived from QUEST1/QUEST2/QUEST3 legacy datasets. (See below for section 8: Legacy Data Conversion Plan and Report Appendix.)</p> <p>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</p> <p>QRS03.ADQS.DTYPE replacing the value 'MAXIMUM' by 'WC' when AVISITN=7777; 'MINIMUM' by 'BC' when AVISITN=5555</p>	BC, WC

5.2.6 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 the 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 the 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.

- For study QRS01, the overall response was assessed by the investigator at Cycle 4 Day 1, 1-month follow-up and 3-month follow-up.
- 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'.
- For study QRS03, the best overall response across study visits was provided by the investigator (data cutoff: 01Sep2021).

Parameters created for analysis:

Overall response after last dose (PARAMCD= "OVRESP1P"): This parameter was derived for the analysis of Overall Response Rate (ORR).

- 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.

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.

- For study QRS03, overall response after last dose was set to the best overall response provided by the investigator (data cutoff: 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 who received the study drug (QRS-MED2022) at each visit cycle.

5.2.7 ADTR – Tumor Measurement Analysis Dataset

This dataset was created for the purpose of creating all tables relating to organ examination. For study QRS02, the SDTM TR domain and ADSL, this was done by merging unique key variables since this is a multiple record per subject dataset and legacy datasets for data integration. The ADTR dataset from study QRS03 and legacy datasets BLTTEST, TRESULT from study QRS01 that are transformed per LDAP (see Appendix 8) were 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.

5.2.8 ADTTE – Time to Event Analysis Dataset

This dataset was created for the purpose of creating all Time-to-Event related tables, figures, and listings. Integrated ADTTE was produced from the SDTM CE, CM, QS, SV domains from study QRS02, and the ADQS, ADTR and ADSL datasets from studies QRS01 and QRS03.

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. The 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 ITTISEFL population.

6. Data Conformance Summary

6.1 Conformance Inputs

Question	Description
Software name and version used for the integrated dataset validation	Pinnacle 21 Enterprise v 4.1.4 Validation Engine Version: 1907.2
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 the FDA as there are no validation rules available for integrated studies.
Software name and version for the Define-XML validation	Pinnacle 21 Enterprise v 4.1.4, Validation Engine version 1907.2, Define-XML v2.0
Version of the validation rules (i.e., CDISC, FDA, PMDA) for the Define-XML	ADaM IG version 1.1 for the FDA

Provide any additional compliance evaluation information:

Not Applicable

6.2 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		14	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		101	RACE is a non-extensible codelist. However, RACE=OTHER is populated if race was collected via the 'Other, Specify' field in the CRF. As per CDISC/SDTMIG 3.2, Section 5 Models for Special-Purpose Domains, Demographics (DM), if the race was collected via an 'Other,

Dataset	Rule ID	Diagnostic Message	Severity	Count	Explanation
					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		105	RACE is a non-extensible codelist. However, RACE=OTHER is populated if race was collected via the '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		1	For study QRS01, source data is in legacy format, converted to ADaM IG 1.1. Hence, no SDTM data is available.
GLOBAL	AD1036	Traceability rules not executed due to missing EX dataset		1	For study QRS01, source data is in legacy format, converted to ADaM IG 1.1. Hence, no SDTM data is available.

7. 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.

7.1 Integrated ADaM Programs

Program Name	Dataset	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	

7.2 Integrated Analysis Output Programs

Program Name	Output Number	Title	Input
T_14_2_1_eff	14.2.1	Summary of Efficacy	ADSL, ADTTE

7.3 Macro Programs

Program Name	Purpose
viswin.txt	Visit Windows creation for record selection
sumn.txt	Counts of subjects per population

8. Appendix

Not Applicable

9. Legacy Data Conversion Plan and Report Appendix

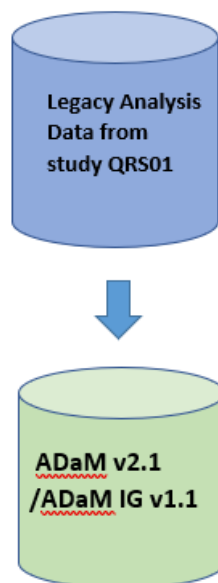
1. Purpose

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.

2. Conversion Data Flow

The legacy data was converted to the 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.

3. Converted Data Summary

Study QRS01 started before 17 December, 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 a mapping specification and programming of the ADaM SAS datasets, the Pinnacle21 validator was run to check compliance with 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

3.1 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 ADaM IG v1.1 to create ADSL based on the legacy analysis data. Here is a summary of the variable changes:

- Subject IDs from legacy analysis data are in non-standard format; for example, subjects 001100, 001362 and 002134 are remapped to USUBJID: QRS01-001-100, QRS01-001-362 and QRS01-002-134, respectively, for data integration.
- The original population flags were numeric. The numeric values were converted from 1 to Y and 0 to N.
- The Define-XML shows how variables were renamed from the legacy data to the ADaM IG 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.
- Originally, phases were referred to as periods in the legacy analysis data but 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.
 - 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 Withdrew Consent	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

Legacy Analysis Data Value	CSR Reported Value	ADSL.DCSREAS
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.
- The legacy questionnaire datasets were already in a similar structure to the BDS, but the variables were changed to be ADaM IG v1.1 compliant where necessary. The Define-XML has codelists for PARAM and PARAMCD.
- Within ADCM, the coding from the legacy dataset has been remapped to the WHO Drug coding variables as per 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 in ADaM ADCM with no imputation.

4. Outstanding Issues

No outstanding issues to report.