

Clinical Study Data Reviewer's Guide

LDCP, Inc.

Study LDCP-888-035

cSDRG Template Version 2018-11-01

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1. Introduction

1.1 Purpose

This document provides context for tabulation datasets and terminology that benefit from additional explanation beyond the Data Definitions document (define.xml). In addition, this document provides a summary of SDTM conformance findings as well as details regarding legacy data tabulation conversion to SDTM.

1.2 Acronyms

Acronym	Translation
aCRF	Annotated Case Report Form
DLBCL	Diffuse Large B-Cell Lymphoma
eCRF	Electronic Case Report Form
eDT	Electronic Data Transfer
IRC	Independent Review Committee

1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	SDTM v1.4/SDTM IG 3.2
Controlled Terminology	2017-09-29
Data Definitions	define.xml v2.0
Medications Dictionary	WHO Drug September 2017
Medical Events Dictionary	MedDRA v20.1

2. Protocol Description

2.1 Protocol Number and Title

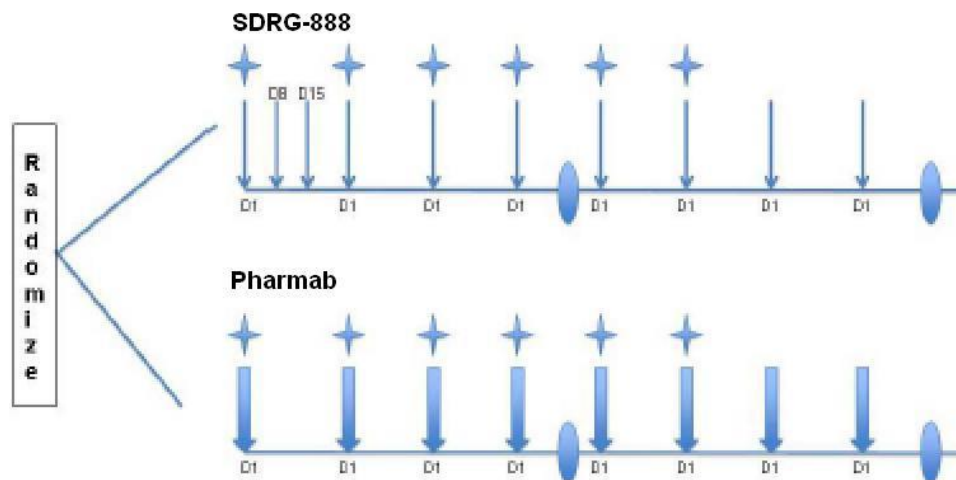
Protocol Number: LDCP-002A

Protocol Title: A Phase III, Multicenter, Open-Label, Randomized Trial Comparing the Efficacy of LDCP-888 in Combination with Investigator's Chemotherapy Regimen of Choice Versus Pharmab and Investigator's Choice Chemotherapy Regimen in Previously Untreated Patients with Diffuse Large B-Cell Lymphoma (DLBCL)

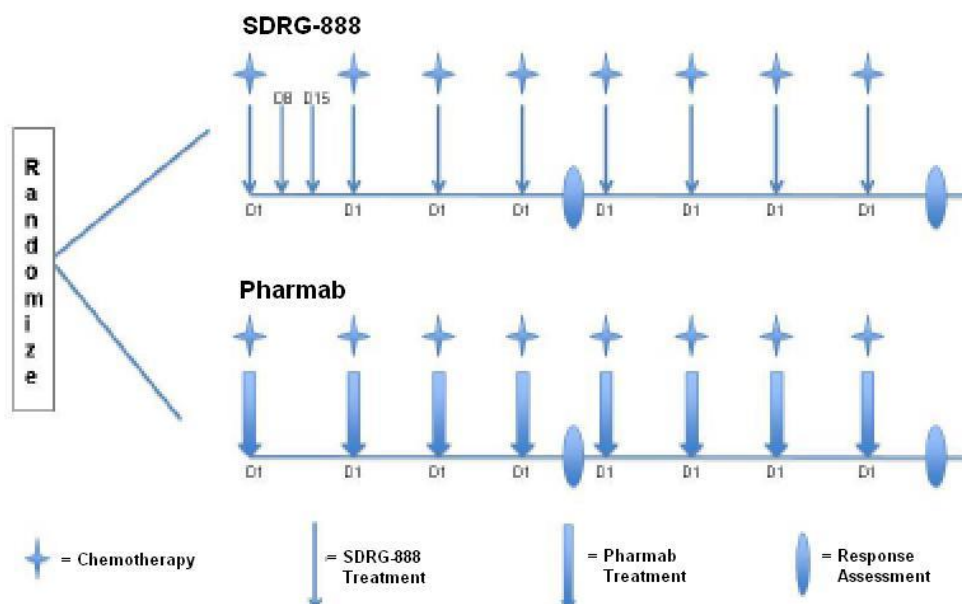
Protocol Versions: LDCP-002A

2.2 Protocol Design

1. SDRG-888 or Pharmab in for 8 Cycles in Combination with Chemotherapy for 6 Cycles



2. SDRG-888 or Pharmab for 8 Cycles in Combination with Chemotherapy for 8 Cycles



2.3 Trial Design Datasets

Are Trial Design datasets included in the submission? Yes

Dataset	Dataset Label
TA	Trial Arms
TE	Trial Elements
TV	Trial Visits
TI	Trial Inclusion/Exclusion Criteria
TS	Trial Summary

2.3.1. TA – Trial Arms

The primary analysis compares LDCP-888 versus Pharmab. The protocol design in Section 2.2 has been represented using four trial arms in order to differentiate subjects receiving six cycles of chemotherapy from eight cycles of chemotherapy. ARMCD uses the convention randomized treatment underscore number of cycles of chemotherapy (i.e., S_C6, S_C8, P_C6, and P_C8).

2.3.2. TI – Trial Inclusion/Exclusion Criteria

The trial inclusion/exclusion criteria are fully described in the TI domain.

2.3.3. TS – Trial Summary

The TS domain includes the deprecated parameter Adverse Events Dictionary (AEDICT) to support internal processes.

3. Subject Data Description

3.1 Overview

Are the submitted data taken from an ongoing study? No

Were the SDTM datasets used as sources for the analysis datasets? Yes, but data was up-versioned from SDTM v1.1/SDTM IG 3.1.1 to SDTM v1.4/SDTM IG 3.2. Please refer to the 'Legacy Data Conversion Plan and Report Appendix' for details.

Do the submission datasets include screen failures? No

Were any domains planned, but not submitted because no data were collected? No

Are the submitted data a subset of collected data? No

Is adjudication data present? No

Additional Content of Interest

The SDTM datasets include both CRF data and electronic data for the study.

Key analysis data points include:

- Disease response endpoints: RS domain where RSEVAL = INVESTIGATOR
- Non-protocol-specified anti-lymphoma therapy: CM and PR domains where --CAT = ANTI-LYMPHOMA THERAPY
- Euro-Quality of Life 5-Dimensions: QS domain where QSCAT = EQ-5D
- Safety analysis: AE domain
- Subject deaths: AE domain where AEOUT = FATAL, DS domain where DSSCAT = STUDY DISCONTINUATION and DSDECOD = DEATH

Per protocol, an Independent Review Committee assessed disease response. IRC assessments are located in the TU, TR, and RS domains and identified by --EVAL equal to INDEPENDENT ASSESSOR. The RS domain includes the IRC adjudicated disease response. These observations can be identified by RSEVAL equal to INDEPENDENT ASSESSOR and RSACPTFL equal to Y.

Reference start date was assigned as the date of first randomized treatment for subjects that received at least one dose of randomized treatment.

A CRF collected pregnancy event information; however, no pregnancy events were reported.

3.2 Traceability Flow Diagram

Please refer to 'Legacy Data Conversion Plan and Report Appendix' for the diagram.

3.3 Annotated CRFs

Collected fields that have not been tabulated have been annotated as "Not Submitted". LDCP Inc. collects certain data elements to facilitate operational processes including data cleaning and dynamically creating additional forms in the electronic data capture system. All fields that have been annotated as "Not Submitted" meet this criterion.

Explanation of data fields [Not Submitted]

aCRF page Number(s)	Data Collection Field	Explanation of why [NOT SUBMITTED]
5	Were there any product complaints?	For internal use only.
30	PI Signature Date	Not needed for analysis.

3.4 SDTM Subject Domains

Dataset – Dataset Label	Efficacy	Safety	Other	Custom	SUPP-	Related Using RELREC
AE – Adverse Events		X			X	CM
CM – Concomitant Medications	X	X				AE
DM – Demographics			X			
DS – Disposition			X			
EG – ECG Test Results			X			
EX – Exposure			X			FAEX
FA – Findings About		X				
FAEX – Findings About Exposure			X			EX
FAMH – Findings About Medical History			X			MH
LB – Laboratory Test Results		X			X	
MH – Medical History			X			FAMH
PR – Procedures	X	X				
QS – Questionnaires	X					
RS – Response	X					
SC – Subject Characteristics			X			
SE – Subject Elements			X			
SV – Subject Visits			X			
TR – Tumor Results	X					TU
TU – Tumor Identification	X					TR
VS – Vital Signs		X				

3.4.1. AE – Adverse Events

As the subject receives multiple study medications, AEACN has been assigned to MULTIPLE and the action taken for each study medication has been represented in SUPPAE. Additionally, AEREL represents the causality of both study medications. The causality for each study medication has been represented in SUPPAE.

QNAM	Description
AEACN1	Action Taken with LDCP-888 or Pharmab
AEACN2	Action Taken with Chemotherapy
AEREL1	Relationship/causality to LDCP-888 or Pharmab
AEREL2	Relationship/causality to Chemotherapy

3.4.2. CM – Concomitant Medications

Concomitant medications taken due to an adverse event were collected with the corresponding AE. The relationship between these medications and the AE is defined in RELREC. Non-protocol-specified anti-lymphoma medications can be identified by CMCAT = ANTI-LYMPHOMA THERAPY.

3.4.3. DS – Disposition

Subjects have two observations with DSCAT equal to DISPOSITION EVENT. DSSCAT equal to STUDY DISCONTINUATION indicates the subject's completion status at study exit. DSSCAT equal to the randomized treatment, LDCP-888 or PHARMAB, indicates the subject's treatment completion status.

3.4.4. EX – Exposure

Each LDCP-888 or Pharmab infusion is represented as one observation. If the infusion is interrupted, EXENDTC is the end date/time of the last interruption and the start and end date/times of each segment are in the FAEX dataset. A relationship between the single observation in EX and interruption segments in FAEX has been defined in RELREC. Chemotherapy regimens have been tabulated in the EX domain.

3.4.5. LB – Laboratory Test Results

QNAM	Description
LBCVRESC	Character result in conventional units
LBCVRESU	Conventional unit
LBCVNRLO	Reference range lower limit in conventional units
LBCVNRHI	Reference ranges upper limit in conventional units

3.4.6. MH – Medical History

Historical DLBCL characteristics collected at study entry including the histopathological diagnosis and Ann Arbor stage have been tabulated in FAMH. A relationship between the DLBCL condition in the MH domain and additional DLBCL characteristics in FAMH has been defined in RELREC.

3.4.7. PR – Surgeries and Procedures

PR is a domain that tabulates historical and coincident surgeries and procedures. Spontaneously reported surgeries and procedures are coded with MedDRA v20.1. Non-protocol-specified anti-lymphoma surgeries and procedures can be identified by PRCAT = ANTI-LYMPHOMA THERAPY.

3.4.8. RS – Response

The investigator's assessment of disease response is identified by RSEVAL equal to INVESTIGATOR. The IRC's assessment of disease response is identified by RSEVAL equal to INDEPENDENT ASSESSOR and RSACPTFL equal to Y.

3.4.9. SC – Subject Characteristics

Stratification factors entered by the investigator into IVRS have been tabulated in the SC domain. SCTESTCD for stratification factors is STRATn, n=1-N. Please refer to define.xml for the corresponding values of SCTEST.

3.4.10. TR – Tumor Results

Tumor measurements and qualitative properties performed by the investigator are identified by TREVAL equal to INVESTIGATOR. Tumor measurements and qualitative properties performed by the IRC are identified by TREVAL equal to INDEPENDENT ASSESSOR. A relationship between the measurements and properties in TR and the tumor descriptors in the TU domain has been defined in RELREC.

4. Data Conformance Summary

4.1 Conformance Inputs

Was a validator used to evaluate conformance? Yes

If yes, specify the version(s) of the validation rules:

Pinnacle21 Community v2.2.0, SDTM 3.2

Were sponsor-defined validation rules used to evaluate conformance? Yes

If yes, describe any significant sponsor-defined validation rules:

LDCP Inc. executes a sponsor-defined conformance rule to confirm variable values that are 200 characters have not been truncated.

Were the SDTM datasets evaluated in relation to define.xml? Yes

Was define.xml evaluated? Yes

Provide any additional compliance evaluation information:

4.2 Issues Summary

Dataset	Diagnostic Message	Severity	Count	Explanation
LB	Missing Units on Value	Error	22	Not an error: Lab results for pH and Specific Gravity have no units

4.3 Additional Conformance Details

Dataset	Diagnostic Message	Severity	Count	Explanation
AE	The length of Reported Term for the Adverse Event (AETERM) is 200 characters. Please confirm the value has not been truncated.	Warning	3	LDCP Inc. clinical data management confirmed the reported adverse event term was not truncated. In all cases, the reported term was split for clinical coding per MedDRA. Please refer to Modified Reported Term (AEMODIFY) for the specific term to which Dictionary Derived Term (AEDECOD) applies.

Legacy Data Conversion Plan and Report Appendix

1. Purpose

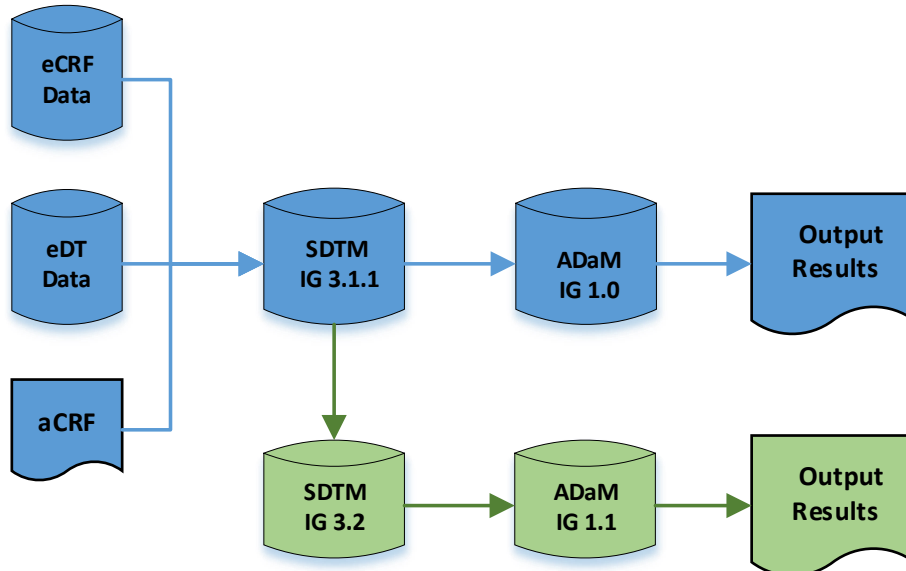
The purpose of this appendix is to document the conversion of legacy tabulation data to SDTM.

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

2. Conversion Data Flow

The legacy data was converted to SDTM as described in the following data flow diagram.

The legacy data was converted from SDTM v1.1/SDTM IG 3.1.1, a version that is no longer supported, to SDTM v1.4/SDTM IG 3.2 as described in the following data flow diagram.



Rationale:

When the study was conducted in 2011, the tabulation data was represented as SDTM v1.1/SDTM IG 3.1.1 and the analysis data was created using ADaM v2.1/ADAM IG 1.0. This SDTM version of the standard is no longer supported per the FDA Data Standards Catalog. The data is considered legacy data and thus, was converted to SDTM v1.4/SDTM IG 3.2 and then ADaM v2.1/ADAM IG 1.1 to be consistent with current CDISC standards requirements listed in the Data Standards Catalog.

3. Converted Data Summary

During authoring of the mapping specification from SDTM IG 3.1.1 to SDTM IG 3.2 up-versioning, CDISC Controlled Terminology (CT) was applied where applicable using the most recent version, 2017-09-29 from the 2011-12-09 version of CT. After authoring of a mapping specification and programming of the SDTM SAS datasets, the Pinnacle21 validator was run to check compliance to SDTM IG 3.2. Any checks that signified a programming issue were addressed and the relevant SDTM datasets were updated.

After resolution of all validation issues that could be fixed, a QC step was performed where the datasets were double-programmed by a separate QC programmer using the mapping spec as a reference. Any fallouts were recorded per the sponsor's SOPs and returned to the SDTM programmer for updates. After confirmation that updates were applied properly, the SDTM data was considered complete and sent to a publishing programmer for creation of the SDTM annotated CRF as well as the define.xml. Each of these tasks included QC steps as well.

The SDTM IG 3.2 datasets were used as input for creation of the up-versioned ADaM datasets. Details pertaining to ADaM and traceability from the new TLFs to the original TLFs are provided in the 'Legacy Data Conversion Plan and Report' section of the ADRG.

3.1 Issues Encountered and Resolved

- Since many domains were added in SDTM IG 3.2, there were some custom domains created for SDTM IG 3.1.1 that were re-mapped to a standard domain in SDTM IG 3.2.

SDTM IG 3.1.1 Custom Domain	SDTM IG 3.2 Standard Domain	NOTES
XP – Surgeries and Procedures	PR - Procedures	Contains data collected for concomitant and protocol-specified procedures.
ZT – Tumor Findings	TU – Tumor Identification TR – Tumor Results	ZT originally contained data collected for tumor identification/location as well as tumor measurements. ZT was split out accordingly to TU and TR as directed in the SDTM IG 3.2.

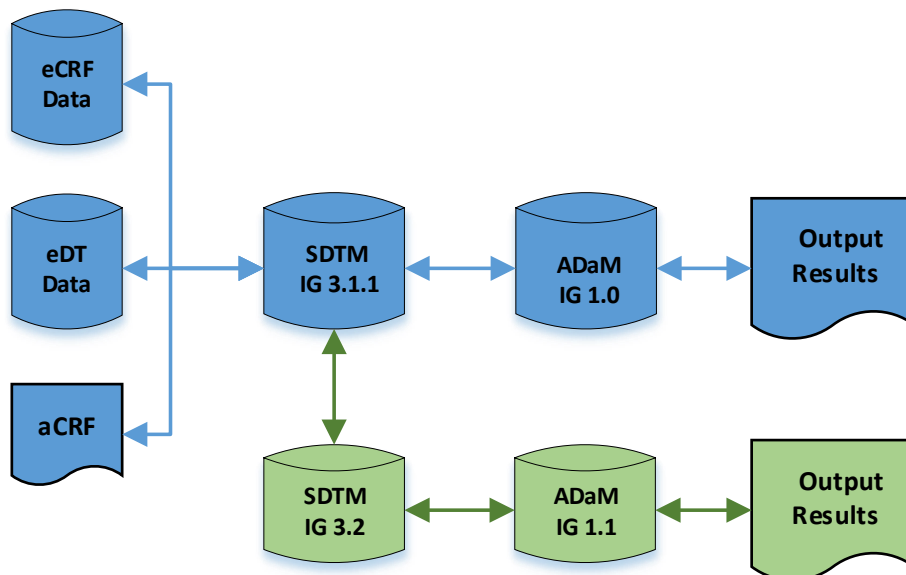
ZA – Clinical Assessments	RS – Disease Response	Contains data collected for tumor response assessments.
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- SUPQUAL variables in the legacy SDTM data were re-mapped to a standard parent variable in SDTM v1.4/SDTM IG 3.2 and controlled terminology was applied, if applicable.

SDTM IG 3.1.1 SUPQUAL	SDTM IG 3.2 Variable	SDTM IG 3.2 Codelist	NOTES
SIDE/Side of Body	--LAT/Laterality --DIR/Directionality	LAT DIR	Laterality and directionality contained together in QVAL were parsed out into --LAT and --DIR
FAST/Fasting Status in Interventions domains (EX, CM, PR)	--FAST/Fasting Status	YN	
AELLT/MedDRA Lowest Level Term	AELLT/Lowest Level Term		
AELLTCD/ MedDRA Lowest Level Term Code	AELLTCD/Lowest Level Term Code		
AEPTCD/ MedDRA Preferred Term Code	AEPTCD/Preferred Term Code		
AEHLT/ MedDRA High Level Term	AEHLT/High Level Term		
AEHLTCD/ MedDRA High Level Term Code	AEHLTCD/High Level Term Code		
AEHLGT/ MedDRA High Level Group Term	AEHLGT/High Level Group Term		
AEHLGTCD/ MedDRA High Level Group Term Code	AEHLGTCD/High Level Group Term Code		
AEBDSYCD/ MedDRA System Organ Class Code	AEBDSYCD/Body System or Organ Class Code		

- MedDRA v14.1 was used to encode adverse events in the legacy data for this study. Terms were re-coded to MedDRA v20.1.
- A proprietary drug dictionary was used to encode data for prior/concomitant medications in the legacy data for this study. Medications were re-coded to WHODrug September 2017.

4. Traceability Data Flow



The legacy SDTM IG 3.1.1 datasets, aCRF, and define.xml have been provided in the 'legacy' folder.

5. Outstanding Issues

- SDTM DS.DSDECOD: When the legacy SDTM IG 3.1.1 DS domain was created, the disposition terms collected on the CRF were not mapped to DSDECOD using the CDISC CT NCOMPLT codelist. A lookup table is provided below to convey the mapping done for subject disposition from legacy SDTM IG 3.1.1 values to SDTM IG 3.2 DSDECOD in the DS domain. For values that do not map directly, the original term captured will be retained in the DSTERM variable.

CRF Collected Disposition Term	Count	SDTM DSDECOD	Count
Completed	62	COMPLETED	62
Need for Excluded Medication	14	OTHER	35
Treatment Unblinded	2		
Non-Compliance With Protocol	2		
Lack of Qualifying Event	5		
Bone Marrow Transplant	12		

CRF Collected Disposition Term	Count	SDTM DSDECOD	Count
Subject Withdrew Consent	16	WITHDRAWAL BY SUBJECT	16
Physician Discontinued Subject	9	PHYSICIAN DECISION	9
Treatment Failure	13	LACK OF EFFICACY	13
Adverse Event	53	ADVERSE EVENT	53
Lost to Follow-Up	3	LOST TO FOLLOW-UP	3
Death	56	DEATH	56