GDO/SP

Up-titration: From complex design to Data/Tables

Penny Pang
Novartis
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Introduction

This slides provides a real example of how we handle dose titration in study from TDM design to output. A dummy study ABC123 is designed as example to illustrate how we:

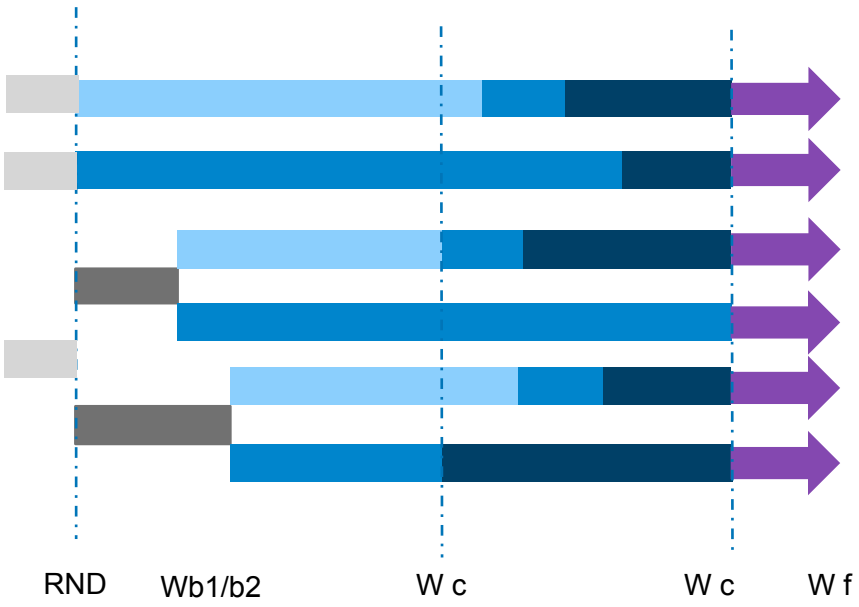
Guidelines

- From study design to TDM
- Major SDTM and ADaM definition
- Table shell for up-titration analysis

Complex Study design

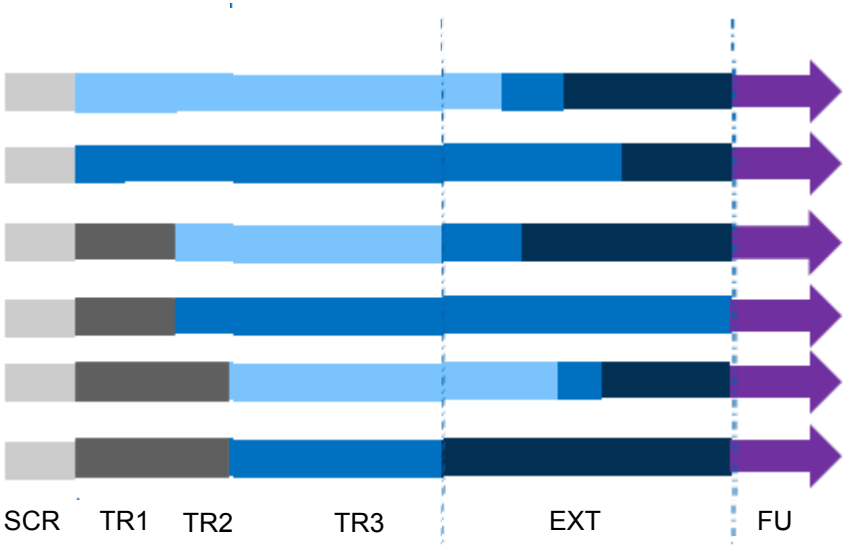
Example study ABC123, long duration, with below special design:

- Switch for PBO
- Rescue
- Up-titration



Study Schema

TDM: The trilogy



Trial design matrix

TAETORD				
1	Screening			
2	PBO A	ABC dose 1 A	ABC dose 2 A	
3	PBO B	ABC dose 2 B	ABC dose 2 B	
4	ABC dose 1 C	ABC dose 2 C		
5	ABC dose 1 initial	ABC dose 2 up-titration		
	ABC dose 2 initial	ABC dose 3 up-titration		
6	Follow up			

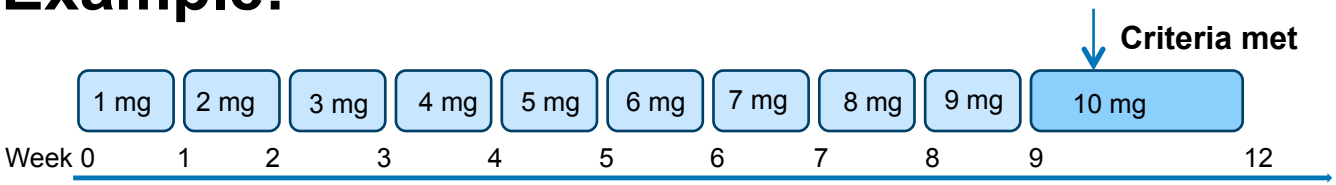
TDM: Up-titration

Standard in IG

- A trial might include a dose titration, with subjects receiving increasing doses on a weekly basis until certain conditions are met. The trial design could be modeled in any of the following ways:
  - using several one-week Elements at specific doses, followed by an Element of variable length at the chosen dose.
  - as a titration Element of variable length followed by a constant dosing Element of variable length.
  - one Element with dosing determined by titration.

TDM: Up-titration

Example:



Design 1

- 1 mg wk 0-1
- 2 mg wk 1-2
- 3 mg wk 2-3
- 4 mg wk 3-4
- 5 mg wk 4-5
- 6 mg wk 5-6
- 7 mg wk 6-7
- 8 mg wk 7-8
- 9 mg wk 8-9
- 10 mg wk 9-12

If it's important to examine side effects or lab values at each individual dose.

Design 2

- 1 mg to 9 mg wk 0-9
- 10 mg constant wk 9-12

If it's important to identify the time to completion of titration.

Design 3

- Dose with titration w1-12

If the titration process is routine and it's of little interest.

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TDM: Up-titration

Design in Data:

- Arm: ABC dose 1 in ext

TAETORD	EPOCH	ETCD	ELEMENT
1	SCREENING	SCR	Screen
2	TREATMENT	PBO1A	Placebo dose 1 A
3	TREATMENT	ABC1B	ABC dose 1 B
4	TREATMENT	ABC1C	ABC dose 1 C
5	EXTENSION	ABC1**I**	ABC dose 1 **Initial**
6	EXTENSION	ABC2**U**	ABC dose 2 **up-titration**
7	EXTENSION	ABC3**U**	ABC dose 3 **up-titration**
8	FOLLOW-UP	FU	Follow up

- Arm: ABC dose 2 in ext

EPOCH	ETCD	ELEMENT
SCREENING	SCR	Screen
TREATMENT	ABC2A	ABC dose 2 A
TREATMENT	ABC2B	ABC dose 2 B
TREATMENT	ABC2C	ABC dose 2 C
EXTENSION	ABC2**I**	ABC dose 2 **Initial**
EXTENSION	ABC3**U**	ABC dose 3 **up-titration**
FOLLOW-UP	FU	Follow up

Additional variables need to be added to define transition between elements.

TDM: Transitions

Standard in IG

- The transition between on element and the next can be thought of as a three-step process.
  - Should the subject leave the current Element?
    - TEENRL for Criteria of ending
  - Which Element should the subject enter next?
    - TABRANCH for branch point
    - TATRANS for within ARM transition(If/then allowed).
    - Otherwise move to next TAETORD
  - What does the subject do to enter the next element?
    - TESTRL in the next element

TDM: Up-titration

Design in TDM:

ETCD	ELEMENT	TESTRL	TEENRL	TEDUR
SCR	Screen	Signing of informed Consent	First dose of iv study drug	P8W
.....	.....	.....	.....	
ABC1**I**	ABC dose 1 **Initial**	First dose of study drug at ext	Last planned assessment ext or First dose up-titrated to dose 2/3	
ABC2**U**	ABC dose 2 **up-titration**	First dose up-titrated to dose 2	Last planned assessment ext or First dose up-titrated to dose 3	
ABC3**U**	ABC dose 3 **up-titration**	First dose up-titrated to dose 3	Last planned assessment ext	
FU	Follow up	Last planned assessment ext	Last planned assessment fu	P4W

TAETORD	EPOCH	ETCD	ELEMENT	TABRANCH	TATRANS
1	SCREENING	SCR	Screen	Randomized to Placebo	N/A
2	TREATMENT	PBO1A	Placebo dose 1 A	Randomized to ABC dose 1	N/A
3	TREATMENT	ABC1B	ABC dose 1 B	N/A	N/A
4	TREATMENT	ABC1C	ABC dose 1 C	N/A	If signs and symptoms are not controlled well, go to ABC2U or ABC3U, else go to ABC1I.
5	EXTENSION	ABC1**I**	ABC dose 1 **Initial**	N/A	If signs and symptoms are not controlled well, go to ABC2U or ABC3U.
6	EXTENSION	ABC2**U**	ABC dose 2 **up-titration**	N/A	If signs and symptoms are not controlled well, go to ABC3U.
7	EXTENSION	ABC3**U**	ABC dose 3 **up-titration**	N/A	N/A
8	FOLLOW-UP	FU	Follow up	N/A	N/A

DATA: SDTM & ADaM

SE & Analysis period in ADSL

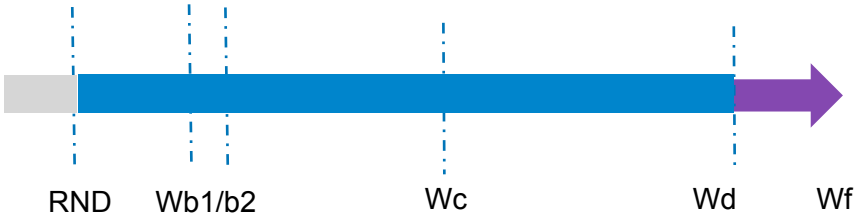
- Generate SE by combine DM.ARM&TA.
- Transfer element start/end date as the start/end date of analysis period.
- Divide the EXTENSION EPOCH to 3 analysis period to identify up-titration.

Analysis Period	Discription
APERIOD 4	Initial treatment in extension
APERIOD 5	1st up-titration in extension
APERIOD 6	2nd up-titration in extension

DATA: SDTM & ADaM

Example:

Subj 1:



SE:

EPOCH	ETCD	ELEMENT	SESTDTC	SEENDTC
SCREENING	SCR	Screen	Date of IFC	Date of RND
TREATMENT	ABC2A	ABC dose 2 A	Date of RND	Date of Wb1
TREATMENT	ABC2B	ABC dose 2 B	Date of Wb1	Date of Wb2
TREATMENT	ABC2C	ABC dose 2 C	Date of Wb2	Date of Wc
EXTENSION	ABC2I	ABC dose 2 Initial	Date of Wc	Date of Wd
FOLLOW-UP	FU	Follow up	Date of Wd	End of study

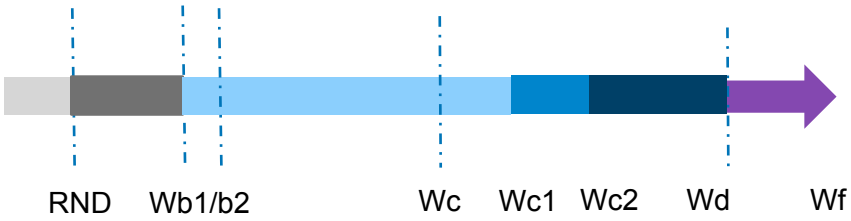
ADSL:

TRT01A	TRT02A	TRT03A	TRT04A	TRT05A	TRT06A
ABC dose 2	ABC dose 2	ABC dose 2	ABC dose 2		

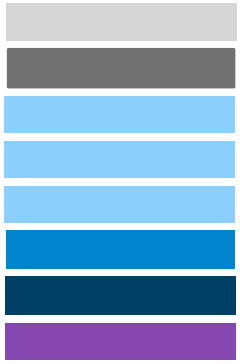
DATA: SDTM & ADaM

Example:

Subj 2:



SE:



EPOCH	ETCD	ELEMENT	SESTDTC	SEENDTC
SCREENING	SCR	Screen	Date of IFC	Date of RND
TREATMENT	PBO1A	PBO A	Date of RND	Date of Wb1
TREATMENT	ABC1B	ABC dose 1 B	Date of Wb1	Date of Wb2
TREATMENT	ABC1C	ABC dose 1 C	Date of Wb2	Date of Wc
EXTENSION	ABC1I	ABC dose 1 Initial	Date of Wc	Date of Wc1
EXTENSION	ABC2U	ABC dose 2 up-titration	Date of Wc2	Date of Wc2
EXTENSION	ABC3U	ABC dose 3 up-titration	Date of Wc2	Date of Wd
FOLLOW-UP	FU	Follow up	Date of Wd	End of study

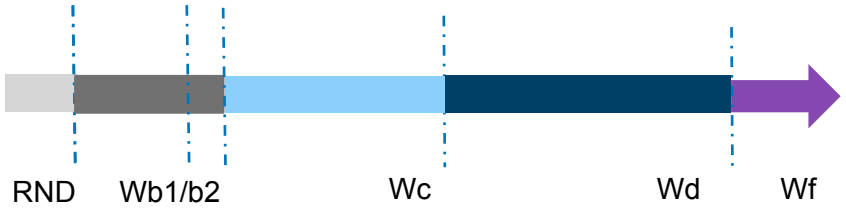
ADSL:

TRT01A	TRT02A	TRT03A	TRT04A	TRT05A	TRT06A
PBO	ABC dose1	ABC dose 1	ABC dose 1	ABC dose 2	ABC dose 3

DATA: SDTM & ADaM

Example:

Subj 3:



SE:

EPOCH	ETCD	ELEMENT	SESTDTC	SEENDTC
SCREENING	SCR	Screen	Date of IFC	Date of RND
TREATMENT	PBO1A	PBO A	Date of RND	Date of Wb1
TREATMENT	PBO1B	PBO B	Date of Wb1	Date of Wb2
TREATMENT	ABC1C	ABC dose C	Date of Wb2	Date of Wc
EXTENSION	ABC3U	ABC dose 3 up-titration	Date of Wc	Date of Wd
FOLLOW-UP	FU	Follow up	Date of Wd	End of study

ADSL:

TRT01A	TRT02A	TRT03A	TRT04A	TRT05A	TRT06A
PBO	PBO	ABC dose 1		ABC dose 3	

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DATA: SDTM & ADaM

Addition variable for up-titration in ADSL

TRTSEQA	Actual Treatment Sequence	N	Derived	Concentration of distinct TRT01A-TRT07A

- Difference between ARM/TRTSEQA
- Relationship

ARM	TRTSEQA
ABC dose 1	ABC dose 1
ABC dose 1	ABC dose 1 - dose 2
ABC dose 1	ABC dose 1 - dose 2 - dose 3
ABC dose 1	ABC dose 1 - dose 3
ABC dose 2	ABC dose 2
ABC dose 2	ABC dose 2 - dose 3
.....	.....

Output: Safety Analysis

Baseline information based on Treatment sequence

	ABC dose 1					PBO-ABC dose 2		
Analysis Sets	ABC dose 1	ABC dose 1-2	ABC dose 1-2-3	ABC dose 1-3	Total	ABC dose 2	ABC dose 2-3	Total
FAS	xx	xx	xx	xx	xx	xx	xx	xx
Safety	xx	xx	xx	xx	xx	xx	xx	xx

Arm

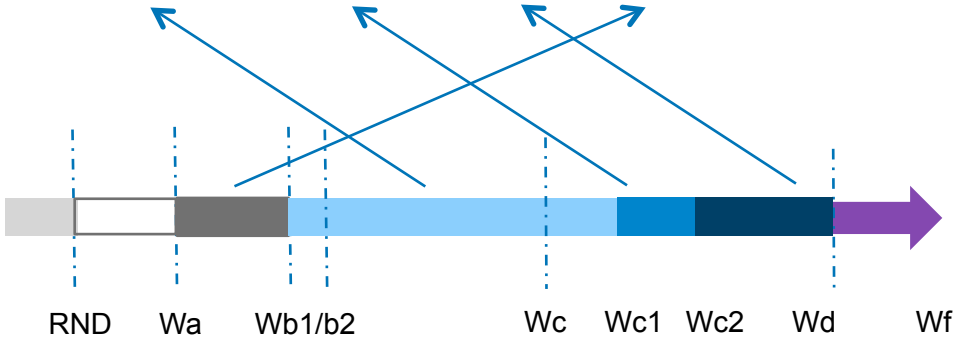
Treatment sequence

Output: Safety Analysis

Event Finding based on Actual treatment

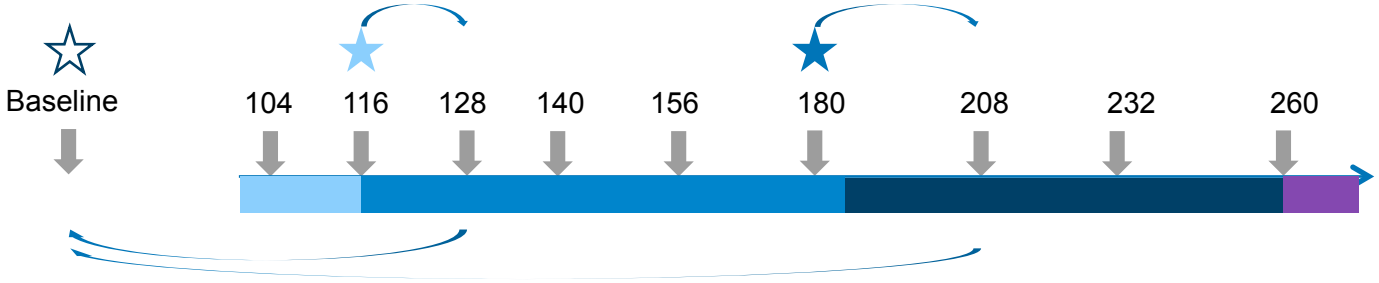
Table 14.3.1-1.2 (Page 1 of xx)
Absolute and relative frequencies for treatment emergent adverse events
by primary system organ class and preferred term - entire treatment period
Safety set

rimary system organ class Preferred term	Any ABC Dose 1 N=xxx n (%)	Any ABC Dose 2 N=xxx n (%)	Any ABC Dose 3 N=xxx n (%)	Any PBO N=xxx n (%)	Any act compare N=xxx n (%)



DATA: BDS structure

Change from Baseline



- Change from Treatment Baseline

  Use CHG based on First dose date

- Change from Up-titration

  ABLFL for last assessment before up-titration

  BASETYPE: up-titration as reference.

  CHG: AVAL – BASE for up-titration visit

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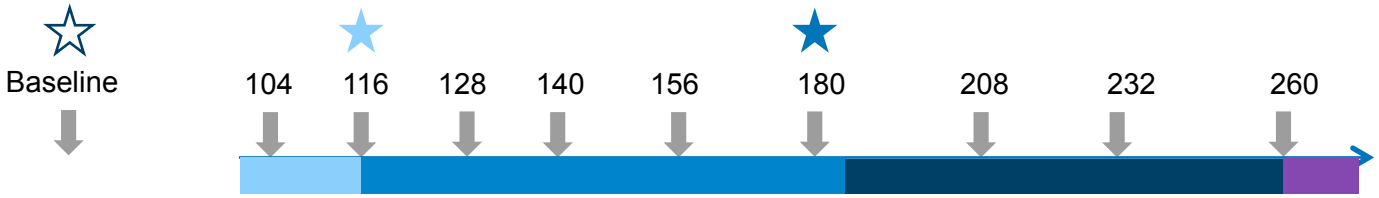
DATA: BDS structure

Visit window



AVISITN	104	116	128	140	156	180	208	232	260
AVISITN	104	0	12	24	40	64			
- up-titration visit						0	24	52	80
AVISITN	104	0	12	24	40	64			
AVISITN						0	24	52	80

- Use the analysis visit window based on ADY
- Use the analysis visit window – up-titration visit
- Remap the Visit window based on ADY up to up-titration

Thank you

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