CDISC Standards for a Breakthrough Therapy

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DCDISC Q2 ‘15 Meeting – June 8, 2015
Outline

• Background
  – FDASIA, breakthrough therapy designation, and electronic data requirements
  – Blinatumomab/BLINCYTO®

• Implementing CDISC for blinatumomab studies
  – Early FDA CDISC feedback
  – CDISC implementation strategy
  – Pre-BLA FDA CDISC feedback
  – Overall benefits of using CDISC (including examples)

• Conclusions
Overview – What This Talk is About

• Consider this a CDISC case study

• I will provide
  – Some background
  – Information on CDISC implementation strategies for our situation
  – An overview of the benefits, lessons learned, and other thoughts about the chosen strategy

• I will NOT go into gory SDTM or ADaM implementation details
  – Except for maybe one example

• I will frequently mention that our Biologic License Application(BLA) was approved in 2.5 months
FDASIA – Food and Drug Administration Safety and Innovation Act

Signed into law on July 9, 2012

Some provisions:

1) Re-enactment of PDUFA and implementation of user fees for other submission types

2) “Innovation” (Breakthrough Therapy Designation)

3) Timeline for the requirement of electronic standardized data
FDASIA & Breakthrough Therapy Designation (BTD)

SEC. 902. BREAKTHROUGH THERAPIES.

(a) IN GENERAL.—Section 506 (21 U.S.C. 356), as amended by section 901 of this Act, is further amended—

(1) by redesignating subsections (a) through (c) as subsections (b) through (d), respectively;

(2) by redesignating subsection (d) as subsection (f);

(3) by inserting before subsection (b), as so redesignated, the following:

“(a) DESIGNATION OF A DRUG AS A BREAKTHROUGH THERAPY—

“(1) IN GENERAL.—The Secretary shall, at the request of the sponsor of a drug, expedite the development and review of such drug if the drug is intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

• BTD allows for the development and review of a drug to be expedited

• A breakthrough therapy must “demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints”

• Evidence must be based on clinical data
FDASIA & Breakthrough Therapy Designation (BTD)

- Since its inception, the BTD has been very popular
- Through March, 2015, FDA has received 293 requests for BTD
  - However, only 82 have been granted (28%)\(^1\)

\(^1\)Breakthrough Therapy Designation: Exploring the Qualifying Criteria, Brookings © 2015
FDASIA & CDISC Standards

- Amends the Food, Drug, & Cosmetics act to require the submission of electronic data, to be specified in guidance.

- This guidance, “Providing Regulatory Submission in Electronic Format – Standardized Study Data”, has since been issued in final form (December, 2014).

- The guidance references the use of CDISC data standards including the SDTM and ADaM.
Background – Blinatumomab

- Blinatumomab is a Bispecific T-cell Engager, or BiTE®, antibody construct
- It is being developed for the treatment of B-cell hematologic malignancies
- It was granted a Breakthrough Therapy Designation by FDA on June 30, 2014 and Accelerated Approval on December 3, 2014—2.5 months after the BLA submission
Background – Blinatumomab

**THE WALL STREET JOURNAL.**

**HEALTH**

Amgen to Buy Biotech Micromet for $1.16 Billion

By PETER LOFTUS
Updated Jan. 26, 2012 4:42 p.m. ET

Amgen Inc. agreed to acquire Micromet Inc. for about $1.16 billion in a deal aimed at strengthening Amgen’s research into cancer drugs.
Blinatumomab Mechanism of Action

- Murine, single-chain bispecific antibody construct directed against the pan–B-cell antigen CD19 and the CD3ε subunit of the T cell receptor complex
- Creates temporary synapse between CD19+ cell and T cell, inducing cytotoxic T cell response to kill CD19+ cell
Blinatumomab Clinical Development History

• The first blinatumomab clinical trial using continuous IV infusion was started by Micromet in 2004

• 6 other clinical trials had been initiated prior to the acquisition of Micromet by Amgen in 2012

• One small CRO based in Munich, Germany, had been responsible for all data management and biostatistical services

• Although the raw data had some similarities to SDTM, there had been no true CDISC implementation at the time of the Amgen acquisition
Prior FDA Feedback

• Early FDA/CDER/OODP (Office of Oncology Drug Products) advice encouraged use of CDISC:
  – Checklist provided
  – SDTM and ADaM IG’s referenced
  – Appendix with General Considerations
• “If a sponsor decides to convert clinical trial data to SDTM that was originally collected in non-SDTM format, it is important to note that the resulting SDTM data should support the accompanying analysis sets and sponsors’ reports”
Prior FDA Feedback

• “It is expected that significant discussions between the sponsor and CDER clinical and statistical reviewers will be necessary to appropriately determine which analysis datasets as well as data content are needed to support application review”
  – [consider this fore-shadowing]
• “Conversion of non-CDISC data to CDISC format the end of the drug development process is more challenging and if pursued, sponsors must ensure that converted SDTM datasets support key analyses contained in the sponsor’s study/integrated reports. In addition, the accompanying analysis datasets should be derived from the SDTM data sets and also must support the analyses contained in the sponsor’s reports”
Prior FDA Feedback

• In short, FDA made it quite clear that they wanted CDISC data
  – But they recognized the challenges in doing legacy data conversions
Implementing CDISC: SDTM Strategy

• Amgen has a sophisticated SDTM implementation platform

• Given that all 7 “legacy” studies were expected to be necessary for an eventual BLA submission, the plan was to convert all raw data for 5 of the 7 studies to SDTM using this platform
  – The other two studies were converted to SDTM by the CRO in Munich

• The process took > 2 years
Implementing CDISC: ADaM Strategy

- 3 of the 7 legacy studies already had TFLs produced
  - For these, ADaM produced for reproduction of “key” efficacy results
  - ADaM also produced for safety data since needed for integration
  - “Linear derivations” were required
    - i.e. the ADaM had to be derived from the SDTM
  - Thorough QC/validation done to ensure CSR reproducability
Implementing CDISC: ADaM Strategy

• 4 of the 7 legacy studies had recently started or did not already have TFLs produced
  – For these, TFLs produced from the ADaM data
  – More ideal and straightforward
Pre-BLA, Type C Data Meeting

• A Type C FDA meeting was held 9-10 months before the planned BLA submission in order gain FDA feedback on the proposed content and structure of the submission, data, and metadata.

• Before the meeting, Amgen provided a mock single-study submission that included:
  – SDTM and ADaM data sets
  – A define.xml and define.pdf
  – A reviewer’s guide
  – Annotated CRFs
Pre-BLA Data Meeting – Feedback

- FDA requested some reviewer-specific data sets:
  1. A response confirmation data set that contained columns for every component of the response criteria as well as key baseline characteristics
  2. A “time to event” data set, somewhat similar to the ADaM TTE structure, but focused only on survival with an additional column for the cause of death
The Response Confirmation Data Set

- Good example where one could simply transpose an ADaM data set in the Basic Data Structure (BDS)

- In ALL/AML, a CR (complete remission) response consists of:
  - Bone marrow blast percentage
  - Platelet counts
  - Neutrophil counts
  - No signs of disease

- These existed as separate parameters
“Horizontalizing” the Basic Data Structure

• Each component of the response criteria can be transposed from a row to a column.
• This can be done for each visit or just the first visit where a response occurred.
“Horizontalizing” the Basic Data Structure

• This is a fairly common request
• Rather than requiring customized programming, it can be automated:

```plaintext
data adrs;
set library.adlb;
  where paramcd='BM_BLSTP' or paramcd='PLT' or paramcd='NEUGRABS';
run;

%horizontalize(indata=adrs,
  outdata=adrsconf,
  xposeby=paramcd,
  carryonvars=adt,
  sortby=subjid avisitn);
```
“Horizontalizing” the Basic Data Structure

Components of the response criteria have been transposed from rows to columns.
“Horizontalizing” the Basic Data Structure

• For our implementation a macro was *not* used

• Having such a tool could prevent the need for customized “views” for reviewers

• Other examples where this transposition can come in handy:
  – Evaluating central versus investigator assessments (e.g. for PFS) side-by-side
  – FDA Anti-viral Guidance…
“Horizontalizing” the Basic Data Structure

Rather specific guidance on a very horizontal data structure that is primarily used for clinical review purposes

Breakthrough Therapy Submission

• Subsequent to the Type C “data meeting”, a BTD application was submitted

• The FDA requested data sets to confirm the information in the application:
  – Basic demographics, disease history, prior therapy
  – Blinatumomab exposure
  – Subset of laboratory data
  – Efficacy dataset with one row per subject
    • (very non-ADaM)

• A define file was requested for all submitted data sets
Breakthrough Therapy Submission

• The BTD application was approved within (the allotted) 60 days of submission

• During and shortly after the BTD application review, the FDA accelerated certain activities normally done after a BLA submission:
  – Close review of the pivotal trial data
  – Investigator site inspections
  – Amgen inspection
Biologics License Application

• The BLA was submitted within 3 months of the BTD
  – Application was submitted on September 19, 2014 (81 days later)

• FDA approval of the BLA occurred within 3 months of the BLA submission
  – Application was approved December 3, 2014 (only 75 days later)
Amgen snags a lightning-fast approval for its leukemia immunotherapy

December 3, 2014 | By Damian Garde

The FDA approved Amgen’s (AMGN) new leukemia treatment more than 5 months ahead of schedule, green-lighting the first contender among a new class of immunotherapies that promise to change the standard of care in blood cancer.

FDA News Release

FDA approves Blincyto to treat a rare form of acute lymphoblastic leukemia

First anti-CD19 drug to receive agency approval

For Immediate Release

December 3, 2014

Release

The U.S. Food and Drug Administration today approved Blincyto (blinatumomab) to treat patients with Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (B-cell ALL), an uncommon form of ALL.
Benefits of Using CDISC

• It is not clear whether the use of CDISC standards helped to accelerate FDA’s review of the BLA

• However, there were several advantages

• Use of CDISC standards facilitated:
  – Data integration
  – Generation of safety narratives
  – Rapid response to questions
Benefits of Using CDISC – Safety Narratives

The JMP Clinical safety narrative utility formed a basis of what became customized/programmed narratives.
Benefits of Using CDISC – Safety Narratives

Subject:
Treatment Arm: BLINATUMOMAB CIV 15 µg/m2/24h, OPEN-LABEL
Drug and Dose at Event Onset: 15 µg/m2/day of BLINATUMOMAB

+ Adverse Event (coded term [reported term]): CATHETER SITE INFECTION [PORT INFECTION]

MeDRA version 17.0 was used.


On 24 JAN 2014 (Day 15) the subject experienced a catheter site infection [port infection] (grade 2) which was considered an adverse event. At the time of the event, the subject was taking 15 µg/m2/day of blinatumomab and had been at this dose for 2 days. The AE occurred 14 days after the first dose of any study medication. Trial medication had an action of drug withdrawn as a result of the event. Concomitant medications administered to treat the event included cefpodoxime and pip/tazo.

Adverse events that occurred within a +/- 3-day window of the onset of the AE included bone marrow failure (grade 2), intention tremor (grade 2), leukopenia (grade 4), nasopharyngitis (grade 1) and neutropenia (grade 4). Concomitant medications taken at the onset of the AE included cefpodoxime, dexamethasone, enoxaparin, fentanyl, filgrastim, glyceryl trinitrate, levothyroxine, macrogol, metoprolol, pantoprazole, potassium, prednisone and valaciclovir. Concomitant medications with partial start or end dates that may have been taken at the onset of the AE included levothyroxine, metoprolol and pantoprazole.

On the closest lab test day on or prior to the start of the events, the subject had the following on-study lab tests with results different than baseline: low absolute monocytes [0.05 10^9/L, range = (0.08 - 0.8), BL = normal], normal albumin [37 g/L, range = (35 - 55), BL = low] and normal alkaline phosphatase [88 U/L, range = (35 - 105), BL = high].

The investigator considered the AE to be probably related to study medication. The final outcome of the event was reported as recovered/resolved on 30 JAN 2014 (Day 21).
Benefits of Using ADaM – Ad Hoc Requests

• Many of our ADaM data had responder flags

• These were extremely helpful for numerous internal and external (regulators, manuscript authors, etc.) data requests:
  – Associations between safety events and response
  – PD markers and response
  – Subgroup analyses

• “Outsiders” new to the program but familiar with ADaM are able to ramp up quickly
Conclusions

• FDASIA implemented many innovations to drug development, including:
  – Breakthrough therapy designation
  – An impending requirement for CDISC data submissions

• In this case study of blinatumomab:
  – BTD definitely helped to expedite the approval process
  – It is unclear whether the use of CDISC standards also helped to expedite the FDA’s approval process
  – However, the use of ADaM has definitely expedited the ability to respond to numerous ad hoc analysis requests
Questions?