COMPARABILITY OF NOVEL THERAPEUTICS: CASE STUDIES FOR A BISPECIFIC T-CELL ENGAGER AND ONCOLYTIC VIRUS

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PRODUCT QUALITY PRINCIPAL
BLINATUMOMAB MECHANISM OF ACTION

Blinatumomab

- Bi-specific T-cell engager (BiTE®) comprised of two antibody variable domains bound via a linker region
- Binds cytotoxic T-cells and CD19+ B-cells resulting in B-cell death
- A single activated T-cell induces lysis of multiple malignant cells analogous to a natural cytotoxic T-cell reaction
- Blinatumomab is approved as a breakthrough therapy for the treatment of (ph-) relapsed/refractory B-cell precursor ALL
Commercial Comparability Strategy

- **Lot Release**
  - Statistical criteria (TIs) for assays with sufficient historical data (n ≥ 5)
  - Specification criteria for assays with limited historical data (n < 5)
  - Process 3, 4, 5 data used for historical range (n=10) comparison to commercial data (n=3)
  - Commercial data plotted versus historical results

- **Characterization**
  - Statistical criteria (EACs) using side-by-side testing of commercial lots (n=3) and P5 lots (n=3)
  - Profile comparison and assessment for new peaks

- **Accelerated Stability and Forced Degradation**
  - Statistical criteria (EACs) for degradation rate; historical data (accelerated) or side-by-side testing (FD)
  - Profile comparison and assessment for new peaks
• All results met comparability criteria
• Orthogonal data can be integral in confirming or disconfirming potential differences from historical trend
  • Some orthogonal methods provide data that may better define actual risk to product quality; MFI can discern silicone oil (spherical) from amorphous particles (non-spherical)

10 µm Particle Counts by HIAC

Triplicate MFI results demonstrate no difference in ≥ 10 µM particle results
• EAC results inconclusive for CEX acidic peaks and not met for DSC T_m 1
  • Differences evaluated for impact to patient safety/efficacy
• Evaluation of differences relies on effective root cause determination and a comprehensive understanding of attribute relevance
  • Lower acidic peak in a commercial lot due to a decreased level of a product-related substance; orthogonal data confirmed level of product-related impurities was comparable
  • Higher melting temperature of commercial lots due to a slight increase in an excipient that stabilizes the protein; no impact to patient as drug product is diluted prior to administration

BLINATUMOMAB COMPARABILITY OUTCOME – CHARACTERIZATION

CEX %Acidic Peaks

DSC T_m of Peak 1
BLINATUMOMAB COMPARABILITY OUTCOMES – ACCELERATED STABILITY AND FORCED DEGRADATION

- All accelerated stability and forced degradation results on DP lyophile met comparability assessment criteria
- Selection of meaningful degradation condition considers linearity of degradation pathway, expected degradation over shelf life and method variability
  - Accelerated stability did not demonstrate degradation for lyophilized presentation
  - Thermal forced degradation condition, included based on previous sponsor commitment, demonstrated non-linear degradation
  - Forced degradation light condition generated meaningful degradation for lyophile
Lot Release:

- **Pre-defined statistical criteria** can be stringent/wide based on amount and/or variability of historical data
  - Limited number of lots (e.g., blinatumomab)
  - Insufficient variability in pre-change data (e.g., single site or lab)
  - Data from Phase 1/2 lots may be included for commercial comparability if representative of material used in Phase 3 (only site and scale changes for blinatumomab)

- **Comparison to historical range is a more science-based approach**
  - Results outside of pre-change range are evaluated for impact to safety/efficacy
  - Understanding of product attribute relevance is crucial to evaluate impact of differences
  - Orthogonal data can confirm/disconfirm differences and may better define actual risk
Characterization and Degradation:

- **Understanding of attribute relevance, method capability and root cause permits proper impact evaluation**
  - Differences may be due to product-related substances with no impact to safety/efficacy (e.g., blinatumomab CEX acidic peaks)
  - Differences may be linked to an unintended consequence of process changes (e.g., blinatumomab excipient concentration impact to thermal transition temperature)

- **Degradation conditions should be relevant to the process, product and presentation**
  - The most meaningful condition(s) and test method(s) should be chosen based on factors such as expected degradation, method variability and attribute relevance
  - Linear degradation pathways are preferable; non-linear pathways are generally more unpredictable
TALIMOGENE LAHERPAREPVEC BACKGROUND

Talimogene Laherparepvec

- Talimogene lahерparepvec is an oncolytic immunotherapy based on attenuated herpes simplex virus type 1 (HSV-1)
- Talimogene lahерparepvec is approved as an orphan drug for unresectable lesions in patients with recurrent melanoma following initial surgery
- Talimogene lahерparepvec infects, replicates within and lyses tumor cells
- Talimogene lahерparepvec expresses hGM-CSF to recruit APCs and potentially stimulate a systemic T-cell response
TALIMOGENE LAHERPAREPVEC PROPOSED MECHANISM OF ACTION

Local Effect: Tumor Cell Lysis

1. Live attenuated virus
2. Selective viral replication and lysis of cancer cells
3. Spread through the tumor by further viral replication and lysis

Systemic Effect: Tumor-Specific Immune Response

4. T-cell activation by antigen-presenting dendritic cell
5. Systemic immune response designed to lead to death of distant cancer cells and protection against relapse

Mechanism of Action
Unique product attributes such as viral protein content, infectivity, hGM-CSF production and hGM-CSF activity

Product attributes have a biological and temporal inter-relationship that must be considered for interpretation of comparability results

- Infectivity impacts in vitro measurements of hGM-CSF expression and % relative potency

The interaction of HSV-1 with cells is complex (e.g., alternative pathways for cell entry, differential expression of viral genes, virus control of cellular processes)

- Data interpretation can be challenging as fundamental research continues to build understanding of HSV-1 biochemical pathways
- Conventional in vitro approaches for protein PK/PD assessments do not apply, which necessitates consideration of in vivo safety/efficacy assessments
### TALIMOGENE LAHERPAREPVEC COMPARABILITY STRATEGY AND OUTCOMES - PROCESS A TO B

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<th>Process A</th>
<th>Non-clinical and Early Phase 1</th>
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<td>Cell line, scale, purification and formulation changes</td>
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<th>Non-clinical, Phase 1 and 2</th>
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- Process B lot release result comparison to Process A phase 1 specifications
  - Differences expected based on extent of changes; all specifications were met
- Characterization assays (side-by-side testing)
  - Potential difference in surface glycoprotein levels; however no impact to efficacy based on non-clinical and clinical data
- Stability at recommended storage was comparable based on visual assessment of data
- Non-clinical assessment (safety and efficacy)
  - Safety and efficacy profiles were comparable

![Graphs showing tumor size over time for Processes A and B with and without injection]
• Process C lot release result comparison to Process B phase 2 specifications
  - Specific activity (PFU/mg total protein) trended higher in Process C due to enhanced clearance of process impurities
• Characterization assays (side-by-side; 3 x 3 lots)
  - Some surface glycoprotein levels slightly increased in Process C with no impact to functional activities
• Accelerated stability (side-by-side testing; 1 x 2 lots) trends were comparable by visual evaluation of data
• Non-clinical assessments (safety and efficacy)
  - Comparable safety and efficacy profiles
TALIMOGENE LAHERPAREPVEC COMPARABILITY STRATEGY AND OUTCOMES – PROCESS C (PRE-MODIFICATION) TO PROCESS C (POST-MODIFICATION)

- Post-change DS and DP lot results (n=3 per SKU) compared to specifications and historical pre-change data
  - Majority of results within historical range; some results were outside of range due to limited pre-change data set, but within expected process variability
- Characterization assays (side-by-side; 3 x 3 lots)
  - Characterization data were comparable based on visual evaluation of data
- Accelerated and stressed stability (side-by-side; 4 x 3 lots)
  - Stability trends were comparable between processes by visual evaluation of data
Comparability Strategy:
• Holistic approach for interpretation of data is warranted when product attributes have a biological and temporal inter-relationship
  • Results for individual assays must be evaluated in the context of the full data set in building conclusions
  • Statistical approaches for individual assay results have limited value

• Comparability strategy/evaluations may be influenced by complexity of the mechanism of action and current knowledge based on fundamental research
  • Talimogene laherparepvec requires multiple in vitro cell-based methods to evaluate mechanisms of action
  • Orthogonal data from multiple assays was used to assess impact of minor differences in some talimogene laherparepvec surface glycoproteins
    – Fundamental knowledge on the role of all HSV-1 surface glycoproteins and the basal levels correlating to functional activity continues to mature
    – When necessary, inclusion of safety/efficacy assessments for talimogene laherparepvec comparability addresses lack of knowledge regarding biological relevance of certain attributes
COMPARABILITY LESSONS LEARNED

- The value of statistical acceptance criteria is limited in some circumstances
  - Extent and variability of historical data may result in inappropriate statistical AC
  - A holistic interpretation of data for attributes that are inter-dependent results in conclusions grounded in scientific understanding of the molecular mechanism of action

- Comprehensive process and product knowledge inform appropriate comparability strategy and data interpretation
  - Knowledge on criticality of attributes on safety/efficacy, process impact on attributes and product degradation leads to appropriate testing, comparisons and evaluation of differences
  - In cases where there are potential gaps in knowledge (e.g., Talimogene laherparepvec glycoproteins), additional data or assessments can potentially fill those gaps
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