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INMAZEB™ Case Study: Industry Perspective

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AGENDA

- INMAZEB* Background
- Key Milestones
- Potential Differences Compared to Standard Process
- Communication of Review Issues

Information sourced from FDA summary basis of approval accessible at: Drugs@FDA: FDA-Approved Drugs

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INMAZEB Background

- A cocktail of three monoclonal antibodies of similar structure, (atoltivimab, maftivimab and odesivimab, also known as REGN-EB3) that bind to different, non-overlapping epitopes on *Zaire ebolavirus* glycoprotein

- Development initially based on Animal Rule pathway

- Pamoja Tulinde Maisha (PALM) randomized controlled trial was stopped early (Aug 2019) because REGN-EB3 was superior to control arm (ZMapp) in preventing death
    - Jointly sponsored by the National Institutes of Health (NIH) and the Institut National de Recherche Biomédicale (INRB) in the DRC

Key Milestones

- First in Human Healthy Volunteer Study Initiated: May 2016
- Orphan Drug Designation Granted: 14 Jul 2016
- Breakthrough Therapy Designation Granted: 03 Sep 2019
- Rolling Review Granted: 02 Oct 2019
- BLA Submission: 25 Feb 2020 ⟹ **PDUFA Date: 25 Oct 2020**
- Mid-cycle Meeting: 08 Jun 2020
- Late-cycle Meeting: 31 Aug 2020
- **Approval Date: 14 Oct 2020**

Drug Approval Package (Drugs@FDA)

Standard Process (Review from 2018)

FDA Application Review Files

- Summary Review (PDF)
- Officer/Employee List (PDF)
- Office Director Memo (PDF)
- Medical Review(s) (PDF)
- Chemistry Review(s) (PDF)
- Pharmacology Review(s) (PDF)
- Statistical Review(s) (PDF)
- Microbiology Review(s) (PDF)
- Clinical Pharmacology Biopharmaceutics Review(s) (PDF)
- Risk Assessment and Risk Mitigation Review(s) (PDF)
- Proprietary Name Review(s) (PDF)
- Other Review(s) (PDF)
- Administrative Document(s) & Correspondence (PDF)

Integrated Assessment (INMAZEB Review)

FDA Application Review Files

- Product Quality Review(s) (PDF)
- Multi-Discipline Review (PDF)
- Proprietary Name Review(s) (PDF)
- Officer/Employee List (PDF)
- Other Review(s) (PDF)
- Risk Assessment and Risk Mitigation Review(s) (PDF)
- Administrative and Correspondence Documents (PDF)

Differences Compared to Standard Process

- Applicant requested to complete a protocol overview and conduct form which was included in the integrated review document

15. Trial Design: Additional Information and Assessment

Note: The protocol synopsis was provided by the Applicant. Cross-references in this section are therefore not consistent with the remainder of the review.

1. Protocol Overview and Conduct

Applicant:	Regeneron Pharmaceuticals, Inc.
Drug Name:	Atoltivimab, maftivimab, and odesivimab-ebgn (also known as REGN-EB3 and REGN3470-3471-3479)
Indication:	Treatment of *Zaire ebolavirus* Infection
Protocol Title:	The PAmoja TuLinde Maisha (PALM) study: A Multicenter, Multi-Outbreak, Randomized, Controlled Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients with Ebola Virus Disease
Source of Information:	1) PALM randomized controlled trial (RCT) Protocol Version 7.0
	2) PALM RCT National Institute of Allergy and Infectious Diseases (NIAID) SAP version 2.0
	3) Regeneron PALM RCT SAP (Original, November 26, 2019)
	4) PALM RCT clinical study report (CSR)

Communication of FDA Review Issues

- Per the integrated review document, FDA identified 8 key review issues: 5 related to benefit and 3 related to risk
- All but 3 of the key issues noted in the integrated review were shared with the Applicant, most of the issues shared were addressed via postmarketing requirements/commitments and product labeling

Review Issues - FDA Internal Discussion Only
Use of an investigational drug, ZMapp (based on results of PREVAIL II), as an active control versus optimized standard of care alone
Adequacy of clinical experience with pediatric subjects
Lack of clinical experience with REGN-EB3 for treatment of EBOV acquired by routes other than natural transmission

Timing of Communications

- Information Requests received on an ongoing basis

- First round of PMR/PMC and labeling comments received prior to late-cycle meeting (LCM) and > 3 months prior to PDUFA date
    - Able to have meaningful discussions at the LCM and before the goal date

Earlier communication for this program may reflect the integrated assessment process, size of INMAZEB data package, and other factors (e.g. ongoing Ebola outbreak)

Overall Impression of Integrated Review Assessment

- Useful to Applicant to understand Agency conversations and differing viewpoints, including those not communicated during review
  - **Example:** integrated summary of clinical virology team position, clinical team position, and signatory position on inclusion of *naturally acquired infection* in labeling
- Potential for earlier communication of key issues
- Interest in seeing if INMAZEB example is reflective of the broader experience as more products fall under the integrated review assessment

Thank You

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