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2021 FDA-Arthritis Foundation Osteoarthritis Drug Development Workshop:

Regulatory Considerations on Biomarkers and Assessment of Long-term Benefit in OA

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- I do not have any financial interest or conflict of interest with any pharmaceutical company

Outline

- Benefit-risk Framework
- Biomarkers in OA: Challenges and Opportunities from FDA Perspective
- Summary

Background

- Significant public health issue, affecting over 30 million people in the US[1]
- Causes significant pain and disability
- Can be a serious disease[2]
- Current treatment options limited to symptomatic therapies and have toxicities
- Unmet need for therapies that would impact the natural history of OA

[1] Castaneda MG, et al., Arthritis Care and Res (Hoboken), 2016 May; 68(5):574-80

[2] https://www.oarsi.org/sites/default/files/docs/2016/oarsi_white_paper_oa_serious_disease_121416_1.pdf

Benefit-Risk Assessment

- Basis for FDA's regulatory decision-making
- Benefit = Clinical Benefit = an improvement in how a patient
  - Feels → Feel
  - Functions → Function
  - Survives → Survival (Joint survival)
- Endpoints in trials of OA treatments need to demonstrate the clinical benefit directly or at least be interpretable with respect to the clinical benefit to be expected

Outcome Measures

- Efficacy assessment
  - Clinical endpoint
    - Measures how a patient feels, functions, or survives
  - Surrogate endpoint
    - A measure expected to predict clinical benefit or harm
  - Biomarker
    - Objective measure of normal biologic process, pathogenic process, or pharmacologic response to an intervention
- Safety assessment
  - Descriptive and empiric
  - Guided by drug class, prior experience, events of interest, etc.

Current Approach of Drug Development for OA

- Drugs approved for OA to date have been approved based on patient-reported outcomes (PROs) assessing two key OA domains
  - Pain → Feel
  - Function → Function

Structural Outcomes in OA: Challenges

- Clinical benefits related to inhibition of structural damage remain elusive to capture in OA and represent an unmet need
  - Structural Outcomes → Biomarker, ? Surrogate
- Treatment affects one of multiple pathways
  - What magnitude, duration of effect on structural outcome is required?[1]
  - Do on-target effects outweigh off-target effects?

[1]After Fleming TR and Powers JH, 2012, Statistics in Medicine, 31.25: 2973–2984

Complex Relationships:
Disease – BM – Clin Outcome

- **Correlation between a biomarker and a clinical endpoint is not sufficient** to demonstrate that an effect on the proposed surrogate endpoint will reliably predict an effect on the clinical outcomes of interest
- **Ideally**, this demonstration would be based on empirical evidence from randomized, controlled comparisons from clinical trials and/or on a comprehensive understanding of the disease process and drug mechanism of action

After Fleming TR and Powers JH, 2012, Statistics in Medicine, 31.25: 2973–2984

Biomarkers in OA:
Challenges

- Endpoints are needed to reliably assess the ability of a product to alter OA disease progression
- Knowledge gaps in the relationship between the structural/pathophysiological elements of OA and the clinical outcomes of OA apply to imaging and other biomarkers
- To use structural outcomes in the benefit-risk assessment, we need to be able to describe the clinical benefit expected from the structural change
- Structural outcomes could be used in addition to clinical outcomes in OA trials

Biomarkers in OA: Challenges

- Approaches to use of structural or other biomarkers in OA trials will depend on level of information available to characterize clinical benefit
  - With less information, structural outcomes may still be useful as adjunct or secondary endpoints
  - To be used as the primary endpoint to support approval, a high level of characterization would be needed about the relationship of the endpoint to the anticipated defined clinical benefit

Biomarkers in OA: Opportunities

- Study designs to assess direct clinical benefit of therapies that inhibit structural damage or target the underlying pathophysiology associated with OA
  - Composite endpoints that capture joint replacement, and “end-stage” joint disease, i.e. the severe, irreversible, intolerable pain or functional impairment
  - Enrichment strategies
    - Models of accelerated OA
    - Trials in subjects prior to knee replacement
  - Innovative clinical trials, i.e. platform, pragmatic trials

Summary

- Complex relationship between pathophysiology, structural damage, and clinical outcomes in OA

- Ultimately, the goal of OA treatments is to provide **clinical benefit to the patient**
  - Goal of clinical trials is to demonstrate this benefit

- FDA recognizes the important public health need in OA and wants to collaborate with sponsors and other stakeholders to bring safe and effective treatments for OA to market

Key References

- OA Guidance
  - https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071577.pdf

- OA Patient-Focused Drug Development (PFDD)
  - https://www.arthritis.org/Documents/Sections/Science/OA-Voice-of-the-Patient-Report.pdf

THANK YOU!


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