2021 FDA-Arthritis Foundation Osteoarthritis Drug Development Workshop:
Regulatory Considerations on Biomarkers and Assessment of Long-term Benefit in OA

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• The materials presented are available in the public domain

• 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
  - Functions
  - Survives
- 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
  - 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

• 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
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.
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

• OA Patient-Focused Drug Development (PFDD)
THANK YOU!