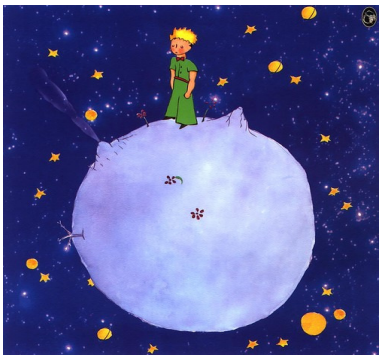
INDUSTRY PERSPECTIVE OF NEEDS OF THE FIELD

Marie-Pierre Hellio le Graverand

Pfizer Primary Care

Objectives

- *Why don't we currently have an approved DMOAD? There have been numerous failed trials and we have learnt from each one yet at this point nothing has been approved.*
- *Include issues such as regulatory hurdles, tissue target selection, translation from preclinical models to clinical trials, early selection of good candidates, and critical issues of timing in respect to the development pathway and patent life of products.*
- *Provide these insights from an imaging barrier perspective. Provide some commentary on how we might overcome them i.e. what do we need to do as an imaging community to overcome these barriers to facilitate clinical trial breakthroughs for OA?*



Pharmaceutical Industry Perspective

Issues

Pipeline
- Generic competition ties marketable life to patentable life
- Most pharmaceutical companies face patent "cliffs"
- New product approvals are decreasing
- Unprecedented costs to bring products to market

Regulatory
- Increased scrutiny of benefits vs. safety
- Longer term/higher patient number clinical studies required
- Drug review times are increasing

Pricing
- Ability to pay, government price controls, competition with standard of care

Legal
- Drug safety, Generics, Marketing

Public Relations
- Public image issues
- Little public focus on pharmaceutical "wins" for society

How Does Pharma View DMOAD Development?

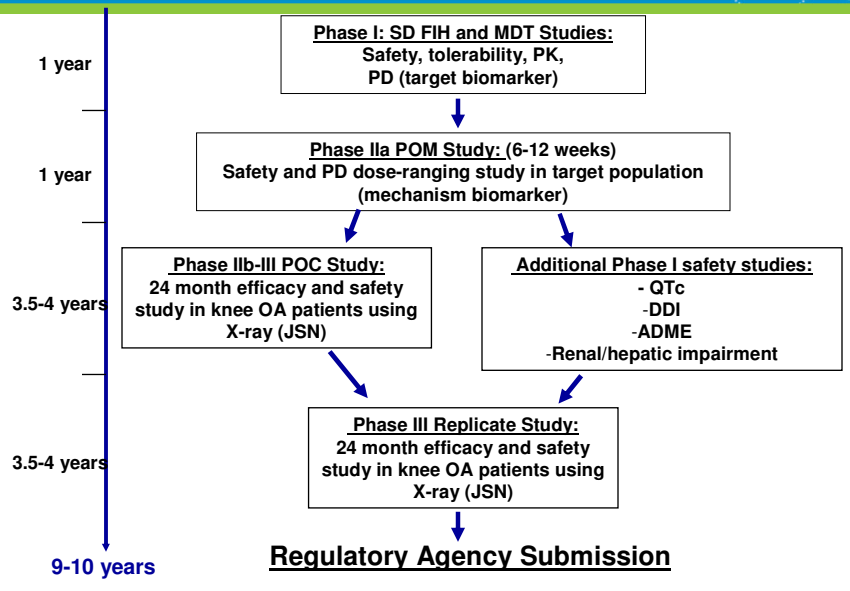
No market precedence, path to PoC and registration unclear, animal model disease relevance unknown, target validation variable, unclear relationship between DMOAD activity & symptomatic/functional benefit

→ Many companies are terminating DMOAD research
- –recent example: Pfizer/Wyeth

→ Many promising opportunities will not be clinically assessed & ultimately patients will not have access to new DMOAD therapies

Critical need for imaging methods to evaluate DMOAD activity in a reasonable time, with reasonable patient numbers at reasonable cost

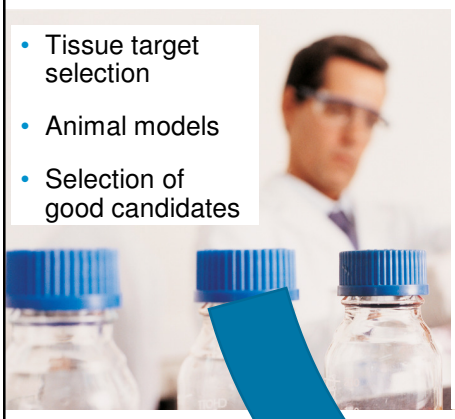
DMOAD Clinical Development: "*the Theory*"

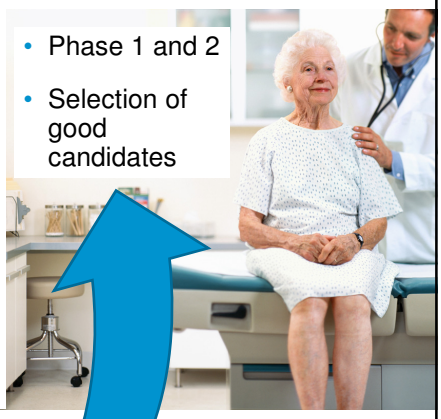


DMOAD Clinical Development: "*the Challenges*"

- How to accelerate development timelines?
  - Strategies to identify and validate new imaging structural endpoints
- What does "clinically meaningful" improvement mean for structure modification?
- How do we translate preclinical/biomarker data to expected efficacy clinically (power assumptions)?
- What constitutes the best clinical POC for a DMOAD?
  - Differentiating between failed study and failed drug
  - What population(s) is/are most appropriate for DMOAD POC study? (positive predictive value)
    - Is rapidly progressing disease the hardest to stop?

Early Clinical Development





Translational Medicine Biomarkers and Imaging

Understand the Human Disease

- *"My fundamental understanding of what's ailing R&D is the fact that true translational medicine is not practiced. R&D in pharma has been isolating itself for 20 years, thinking that animal models would be enough and highly predictive, and I think I want to just bring back the discipline of outstanding translational science, which means understand the disease in humans before I even touch a patient."*

Elias Zerhouni, Radiologist,
President Global Research & Development Sanofi-Aventis,
Former Director of the NIH

Translational Medicine

- 5-Year Biomarker Plan (2004)

Osteoarthritis Biomarker Strategic Plan

Section I: Executive Summary

Osteoarthritis (OA), a degenerative disease that often has a long latent period, is the most common form of arthritis. OA is one of the most widespread chronic health problems, with a major market (US, EU, Japan) prevalence of over 234 million sufferers, and is expected to increase over the upcoming decades as the population ages. In OA, an imbalance in matrix synthesis and breakdown leads to the destruction and eventual loss of articular cartilage, which results in restricted joint movement, joint instability and pain. Current therapies, primarily non-steroidal anti-inflammatory drugs (NSAIDs) and specific COX-2 inhibitors alleviate the mild to moderate pain and inflammation associated with OA. However, they do not protect the articular cartilage and have not demonstrated utility in modifying disease progression. Therefore, agents that prevent the irreversible loss of joint function, reduce tissue damage, and decrease the need for joint replacement would address a major unmet medial need. Hence, current Discovery Research efforts target identification of drug candidates that can modify OA disease progression (i.e., Disease Modifying OsteoArthritis Drugs: DMOADs). However, significant gaps exist in our ability to clinically monitor joint biological and structural changes involved in disease progression. The discovery, development, and validation of appropriate biomarkers are key to addressing these gaps.

To capitalize on our strong DMOAD pipeline, the OA Biomarker Team (a sub-team of the Inflammation Biomarker Team focusing on OA biomarkers) plans to develop imaging and biochemical markers that will facilitate the design of smaller and shorter clinical POC studies and efficacy trials. One of the major gaps in this area is the availability of a biomarker that correlates with OA disease severity or joint structural changes to serve as an Outcome Biomarker for determining inhibitor efficacy. Magnetic resonance imaging (MRI) assessment of cartilage quality, and morphometry (e.g., volume, thickness, surface area and lesion size) offers a potential method for sensitively monitoring small changes in joint structure that could be used as an Outcome Biomarker. Although this technology has not yet been fully validated or accepted by the FDA as a surrogate for the clinical endpoint (e.g., how the patient feels and functions, time to joint replacement), it has the potential to drive the internal decision-making process and significantly shorten the length and sample size of clinical trials. Thus, exploiting this technology and validating its ability to follow disease progression are a top priority.

Even with MRI, a biomarker is needed for early internal decision making before proceeding to longer studies. For this purpose biochemical markers that monitor the target itself or a biological effect downstream of the target are being developed. These markers will be essential for assessing the ability of inhibitors to hit their target and/or block the intended pathway and to select the dose for efficacy studies. Some of these target or mechanism markers, such as matrix catabolites, have also been considered as potential markers of disease severity. However, the levels of matrix catabolites present at any particular time are related to the *rate* of catabolism at that point in time and, thus, would represent the level of disease activity rather than the overall severity of the structural changes. In addition, biochemical assays may represent and measure overall metabolic activities rather than those activities localized to the cartilage. Currently, most available assays have not shown a robust differentiation between OA patients and controls, and correlation with measures of structural progression or clinical symptoms has not been demonstrated yet.

Another approach to decreasing the number of patients required and/or length of clinical trials is to identify a marker that is predictive of the rate of disease progression. Such a marker would enable the identification and inclusion of patients at risk for significant progression within a trial and thus decrease the variability normally observed in the joint structural changes between individuals. In

- FDA Pfizer Meeting (2005)

PFIZER - OA Biomarker Strategy Document

Pfizer Global Research & Development
Osteoarthritis Biomarker Strategy

Briefing Document for Meeting
29 April 2005

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DMOAD Development: "*the Enablers: Biomarkers*"

- Target/Mechanism biomarkers in Phase I-IIa
  - Dose selection and early Go-NoGo decision
- Outcome Biomarkers in place of JSN in Phase II-III
  - Reduction of sample size and length of POC studies
  - Registration endpoints
- Population at risk of progression during treatment period (use of prognosis biomarkers and/or disease models)
  - Avoid failed POC studies
  - Reduction of sample size and duration of POC studies
  - Extrapolation to general OA population

Qualification of Biomarkers *(2001 – Present)*

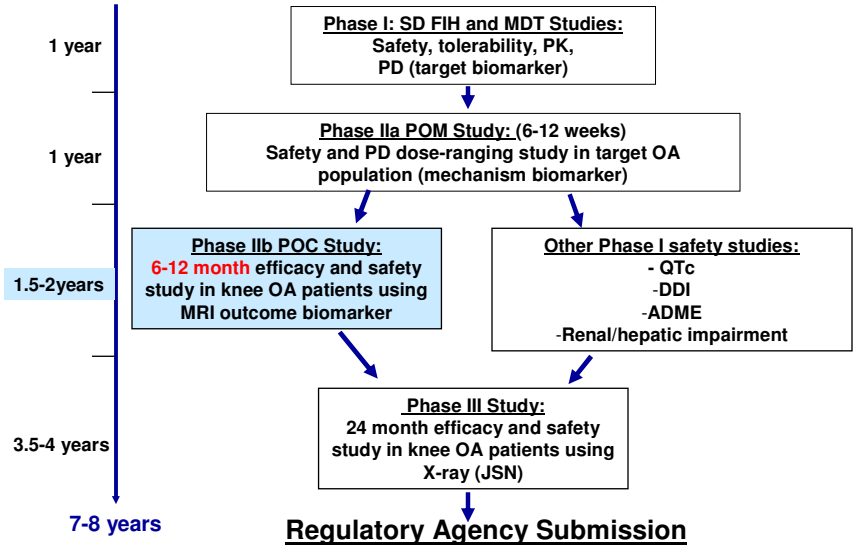
- Longitudinal studies
  - GARP : Genetica Arthrose en Progressie (M. Kloppenburg, Leiden University)
  - KANON: ACL injury (S. Lohmander, Lund University)
  - NIH Osteoarthritis Initiative
  - A9001140 : Obese Women with Knee OA

➔Imaging and biochemical markers

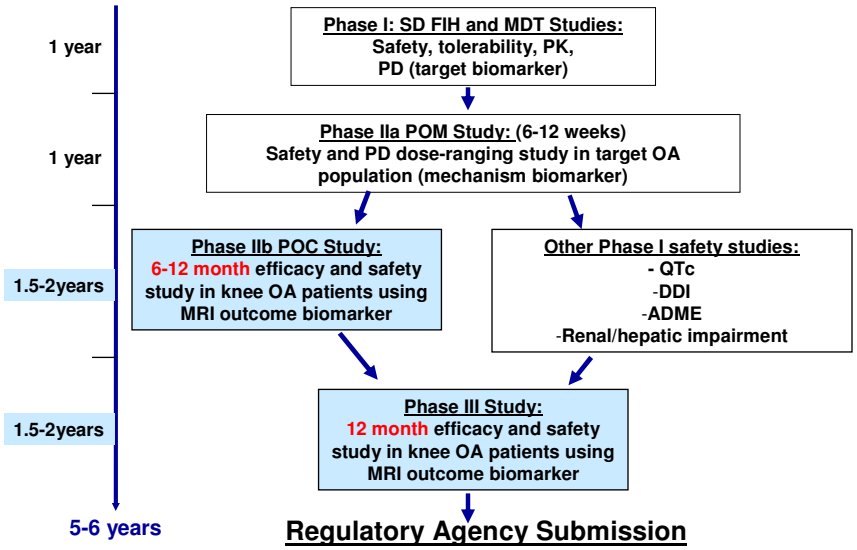
- 1.5 or 3.0 T MRI
  - dGEMRIC, T1, T2, cartilage morphometry (F. Eckstein, VS), semiquantitative scoring (e.g., BLOKS)
- Serum and urine markers
  - Serum: COMP, CTX-I, PINP, PIIANP, CPII, NPII, PIIINP, 3-NT, 15-HETE, and PGE2
  - Urine: TIINE, CTX-II, TINE, TIIINE, Aggrecan fragments, Osteopontin

- Cross-sectional study
  - Weight-bearing MRI (S. Majumdar, UCSF)

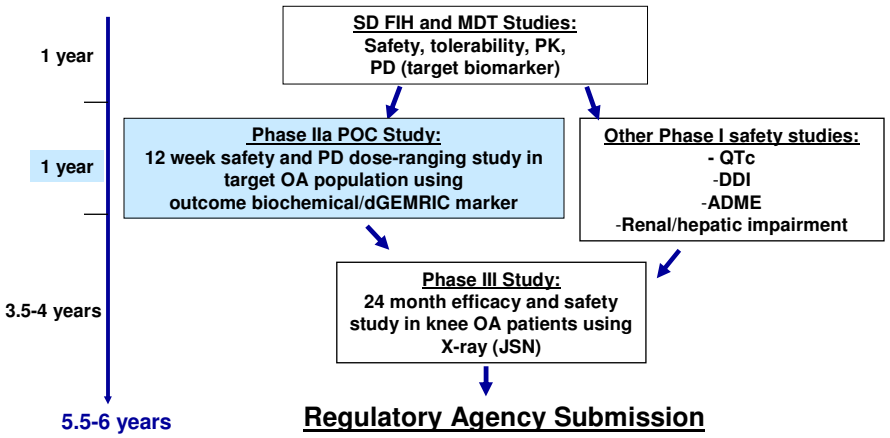
MRI Outcome Markers for POC



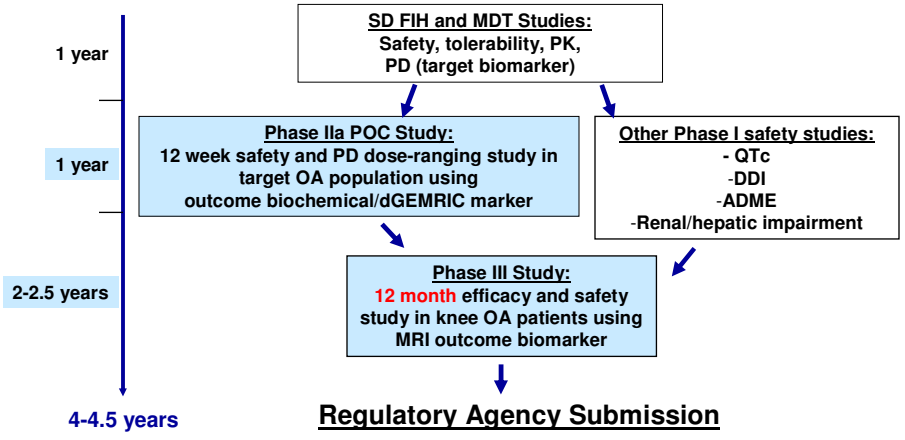
MRI Outcome Markers for POC and Registration



Biochemical Outcome Marker for POC



Outcome Markers for POC and Registration



Key Questions to FDA

- Reasonable or idealistic approach?
- Do outcome biomarkers need to correlate with functional outcome measures?
- Is a functional outcome required for registration?
- What type of functional outcome would be considered acceptable?

DMOAD Development : "*The Reality*"

Cindunistat, a Selective iNOS Inhibitor

1995 / 2002 — 7 yrs
Preclinical Studies
Chemistry, Biology
Pharmacology, Safety

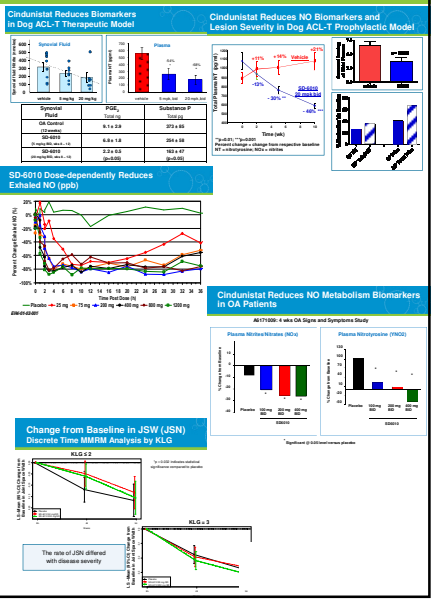
2003 / 2004 — 2 yrs
Phase I
Safety, tolerability, PK,
PD (target biomarker)

2005 — 1 yr
Phase IIa POM Study
Safety and PD dose-ranging study
in target population
(mechanism biomarker)

2006 / 2007 — 4 yrs
Regulatory Scientific Advice
Phase IIb-III POC Study:
24 month efficacy and safety
study in knee OA patients using
X-ray (JSN)

2011 — *Regulatory Scientific Advice*

15 years



De-Risking a DMOAD POC Study and Program *(2006)*

- Optimize study design to minimize upfront investment
  - Enhanced Clinical Trial Designs
    - Interim analyses for futility
    - Adaptive design
- Optimize study design to avoid failed study
  - Highly standardized radiograph methodology
    - Modified Lyon-schuss protocol
  - Select subjects more likely to progress during 24-month treatment period
    - Enriched for KLG3 subjects
    - Excluded subjects with genu valgum/significant genu varum
- Gain agreement from regulators on development plan and study design

POC and Phase IIb/III – A Multi-Purpose Study

POC

- Study designed to demonstrate that iNOS inhibition slows disease progression in OA patients compared to placebo
  - Radiographic Joint Space Narrowing (JSN) as the primary endpoint

Pivotal

- Appropriately designed, executed and analyzed could be considered pivotal
  - If positive, would require 1 replicate study
  - If positive POC but fails statistical rigor to qualify as a pivotal trial, might be considered as supportive to a single pivotal study (EOP2 meeting to confirm)

Exploratory

- Several secondary measures included to explore “Clinical Benefit”
- MRI in a subcohort

Regulatory Scientific Advice

- 2006

- 2011

2006 Regulatory Advice – Key Points

✓ Agreement on Development Strategy

- First 2-year study (Phase IIb/III - POC/pivotal)
  - To demonstrate DMOAD effect using JSN
    - Use of an adaptive design and interim analyses for futility
- Second 2-year replicate study (Phase III)
  - To confirm DMOAD effect (JSN)/ pivotal
- Clinical benefit must be demonstrated for registration
  - Phase IV commitment to demonstrate clinical benefit not acceptable
  - Willingness to accept demonstration in a separate study
  - Secondary (pain, function & medication burden) endpoints acceptable
  - Virtual Joint Endpoint considered exploratory and would require validation prior to registration if to be used for a label claim

2011 CHMP Scientific Advice - Issues

- *"…The proposal to demonstrate clinical benefit based on results of X-ray studies as primary endpoint in combination with one or more clinical endpoints as secondary endpoints is not supported. The choice of a co-primary endpoint should be discussed…*
- *…Taking into account both aspects of efficacy and safety, a study duration of less than 2 years appears not to be justified...*
- *…An overall broad indication claim for treatment of osteoarthritis is expected to be substantiated by data from both the knee and the hip…"*

Learnings from the Cindunistat DMOAD Trial

- Hypothesis: does iNOS inhibition slow OA progression?
- Results

1. Structure Modification
   - Negative study (failed drug): primary endpoint was not met
   - Not a failed study: sufficient progression in placebo group to determine a drug effect
   - Detection of JSN in KLG2 subjects is possible, as early as 1 year
     - With another MOA, one might consider studying the effect of a DMOAD in subjects with less advanced disease
   - Long-term demonstration of efficacy is key
     - An early effect might not be maintained over time
   - *Etiopathogenesis* (biomechanical) versus *pathogenesis* of joint damage
     - Treatment approaches should consider OA as the *failed* repair of mechanically induced joint damage

Learnings from the Cindunistat DMOAD Trial

2. Clinical Benefit
   - Significant placebo response
   - Early versus long-term data

Responsiveness of NSAIDs in Knee OA

	BL Mean (SD)	Percent change from BL	Effect Size	SRM
WOMAC pain	45.0 (21.6)	20.5%	0.55	0.58
ICOAP total	44.8 (20.2)	18.8%	0.53	0.56
ICOAP constant pain	40.7 (22.5)	21.1%	0.46	0.49
ICOAP intermittent pain	48.3 (20.1)	19.9%	0.54	0.55
WOMAC phys. function	47.7 (22.7)	24.7%	0.52	0.58
KOOS-PS	42.3 (13.0)	13.1%	0.53	0.52

M. Bond, A. Davis, S. Lohmander, G. Hawker. Osteoarthritis and Cartilage 20, 6, 2012, 541–547

Responsiveness of Clinical Benefit PROs

	BL Mean (SD)	Percent change From BL	Effect Size	SRM
WOMAC pain	7.6 (4.0)	28.9%	0.54	0.58
ICOAP total	38.8 (22.3)	33.5%	0.62	1.16
ICOAP constant pain	35.2 (24.5)	37.3%	0.54	0.56
ICOAP intermittent pain	41.7 (22.1)	34.2%	0.65	0.63
WOMAC phys. function	27.39 (13.81)	26.8%	0.53	0.59
KOOS-PS	42.6 (14.8)	22.5%	0.65	0.62

Clinical Benefit at 6 Months (IA1)

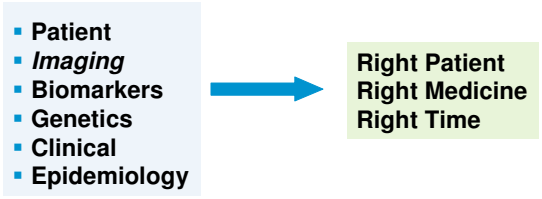
		Cindunistat	
Percent improvement from BL (P-value compared to placebo)	Placebo N=80	50 mg N=71	200 mg N=80
VAS pain	20%	37% (p=0.05)	37% (p=0.08)
Patient Global Assessment of OA	2%	15% (p=0.02)	20.6% (p<0.01)

Demonstration of DMOAD Efficacy

- Demonstration of structure preservation and clinical benefit
  - *M Liang J Rheum 2004*
    - *"JSW is not what people care about; they care about how they feel and what they can do. We need patient-oriented measures. However, the patient-oriented measures available to us are most relevant and useful in advanced knee OA. In fact, almost everything we know about knee OA is derived from patients with advanced disease. To evaluate the possibility of achieving major health effects with an intervention that prevents or delays the onset of knee OA, our outcome measures are insensitive, unresponsive and, basically, of little use"*
- Symptomatic OA versus window of opportunity for pharmacological intervention
  - *M Liang J Rheum 2004*
    - *"Need new knowledge of the determinants of why and how people adapt preventive behaviors or take medications for asymptomatic or barely symptomatic musculoskeletal conditions that take decades to become manifest. We will need cost-effective, sensitive measures for earliest and early OA, and we will need to develop measures of impairment and symptoms that are sensitive to the entire range of progressive OA".*

How to Overcome These Barriers to Facilitate Clinical Trial Breakthroughs for OA?

- Collaborate and develop a research agenda that will address key questions to better understand the human disease



  - Mine existing datasets of longitudinal cohorts
  - Characterize OA phenotypes using both imaging and molecular markers
  - Develop more sensitive methods for image data analysis
  - Develop more sensitive patient-reported outcomes
  - Understand placebo response in long-term trials

Thank You!