Day 1
5 October 2021

Breakout session 2
Regulatory processes and system

Multi-stakeholder workshop
5 - 6 October 2021

Chairs:

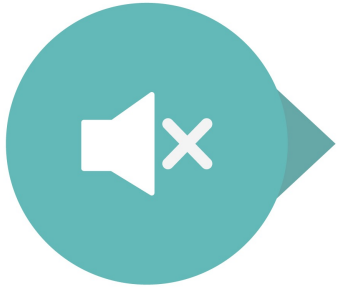
Anja Schiel (EMA SAWP, NoMA)

Lucia D'Apote (Amgen, EFPIA)

As the EU regulatory landscape and policy initiatives continue to evolve, this session will provide a platform for exchange between drug developers, regulators (EMA, CTFG, EU-IN) and other stakeholders to discuss the current regulatory process and system for CCT trial advice and authorisation. The session will use case studies and research on CTT proposals accepted by regulators to highlight learnings and opportunities for regulatory convergence. A panel discussion at the end of the session will provide perspective on policy opportunities from all experts.

House-keeping rules

(For active participants in the Zoom call)



- Mute your sound and video when not speaking

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A Phase 2b Bayesian Adaptive RCT with RAR

Juliana Sholter

Regulatory processes and systems

NF Patients United
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BARC
PPD
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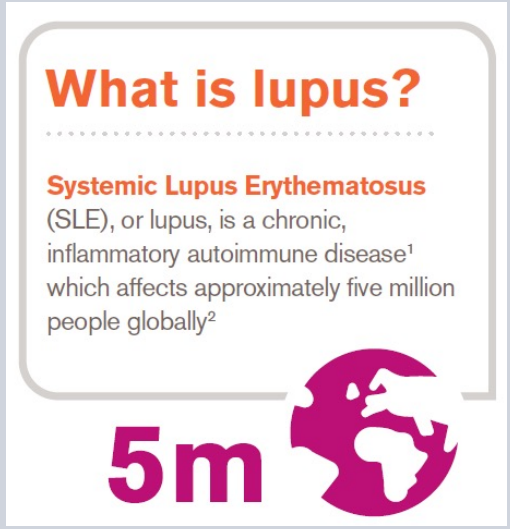
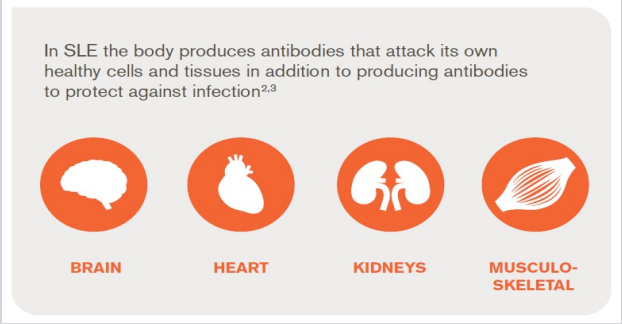
Background: Unmet need and challenges in drug development

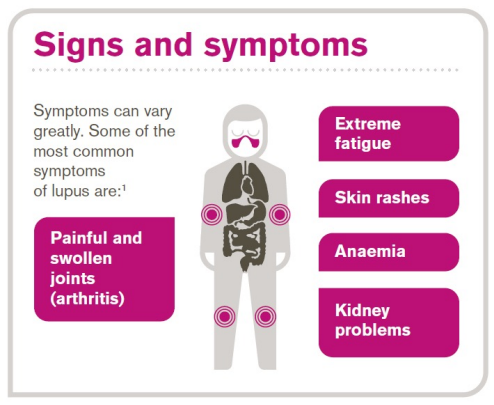
Unmet Need



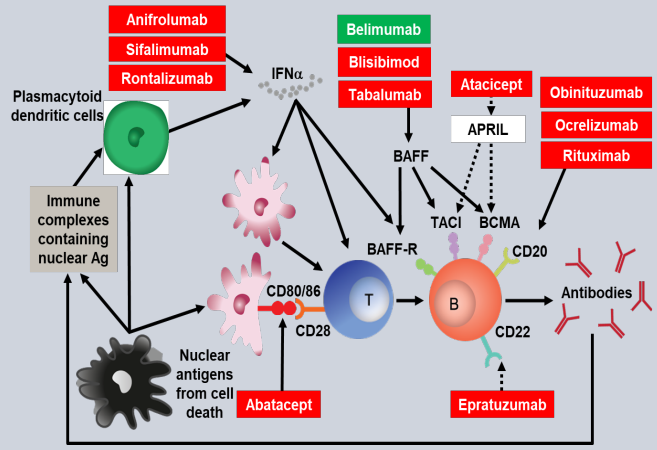
Persistent SLE disease activity is associated with a higher risk of organ damage and mortality[5]

Heterogeneous Disease





Development Difficulty



belimumab, anifrolumab: approved biologics for SLE

Case Study : A Phase 2b Bayesian Adaptive RCT with RAR

Rationale for proposing the adaptive/innovative design features

Response Adaptive Randomization

- Learn from accumulating data from ongoing trial
- Patient centric: reduce exposure to less effective treatment
- Increase efficacy & safety data collection on effective treatment

Interim Analyses for futility

- Stop patient exposure to non-effective treatment
- Reduce the cost of failure
- Shorten development timeline

Final Analysis Bayesian Hierarchical Model

- Dynamic borrowing across the active treatment arms improves estimation of treatment effect
- No underlying dose-response assumptions to reduce bias

US FDA CID Pilot Program

Objectives and Benefits

Supports the goal (under PDUFA VI) of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs. Selection criteria:

- ✓ Intended to provide substantial evidence of effectiveness to support regulatory approval
- ✓ Innovative features of the trial design may provide advantages over alternative approaches
- ✓ Analytically derived properties may not be feasible, and simulations are necessary to determine operating characteristics
- ✓ Therapeutic need (i.e., therapies being developed for use in disease areas where there are no or limited treatments)

Potential benefits from participating in the pilot program:

- ✓ Feedback: Direct feedback from large multidisciplinary team from the agency
- ✓ Knowledge Share: Opportunity to share innovative tools to evaluate complex innovate designs
- ✓ Guidance: Clear guidance on missing pieces of the evaluation

Amgen US FDA Experience through the CID Pilot Program (1 of 2)

Amgen participated in two meetings with FDA to engage in scientific discussions and reach agreement on an innovative study design that is appropriate for a study supporting registration

Meeting Request	Meeting 1	Meeting 2
➢ Requested discussion of the clinical relevance of the potential primary endpoints and formal definition of their estimands ➢ Recommended removing some proposed adaptive elements to reduce the dimensions to be explored in simulation for feasibility and interpretability considerations ➢ Suggested arm-dropping as an alternative to RAR* ➢ Set expectations on operating characteristics, simulation replicates, and nuisance parameters to be explored	➢ Discussed in detail the space of plausible nuisance parameters and combinations required to provide convincing evidence of type I error control and other operating characteristics ➢ Confirmed that BHM* and RAR would not preclude the study from being registrational, however, requested evaluations against multiple alternative designs, analysis methods, and simulation scenarios to demonstrate advantages of the proposed design ➢ Provided feedback on primary endpoint selection and recommended additional criteria to maintain trial conduct and integrity	➢ Confirmed that Amgen had largely addressed concerns and implemented suggestions to demonstrate that the proposed study design was appropriate as a registrational study ➢ Requested further comparison to alternative methods (NDLM, Dunnett) to establish BHM as the favorable method ➢ Requested information to justify for range of control response rate and concordance between adjacent visits ➢ Requested data access plan to be submitted

*RAR: Response Adaptive Randomization
BHM: Bayesian Hierarchical Model

Amgen US FDA Experience through the CID Pilot Program (2 of 2)

Protocol Review and Clinical Study Execution

- Simulation plan expected to be exhaustive, resulting in millions of trial simulations to evaluate design operating characteristics (OC)
- Assessment and summary of design OCs expected to be presented in a concise manner
- Design evaluations for CID program are similar to scope and focus as any proposed complex innovative design proposed
- No specific challenges regarding conducting the clinical trial have occurred in the US
- The study will be conducted globally and is ongoing, (initiated in the US in 2Q2021 and recently initiated in European countries)

Process with Regulators

- Selection for the CID program does not mean the proposed CID is appropriate for regulatory decision making; likewise, not being selected does not mean the proposed CID is unacceptable for regulatory decision making
- By being selected, Amgen participated in two meetings with FDA (one face-to-face, one telecon)
- During both meetings, FDA and Amgen engaged in detailed discussions about the proposed trial design (particular emphasis was placed on comparisons to alternative methodologies)
- Communication with FDA went beyond the two meetings. Although Patient Reported Outcomes were not discussed during the meetings, feedback from the Clinical Outcome Assessments group was received through the CID process

Amgen's EU CTA experience using the same study design (1 of 2)

Regulators in VHP and non-VHP participating countries evaluated a study design that had undergone extensive review and input from the US FDA through the CID pilot program

Study Design Experience

- Although invited through the VHP process, one country decided to not participate in the VHP review, resulting in a VHP and country-level review in parallel
- Amgen received two rounds of written questions from reviewers, including:
  - quality questions
  - clinical questions
- Amgen did not receive any questions pertaining to the statistical aspects of the study design
- The clinical study has been approved in all VHP and non-VHP participating countries

Amgen's EU CTA experience using the same study design (2 of 2)

CTA Review and Clinical Study Execution	Process with Regulators
• One ethics committee (EC) identified issues with the study design that was accepted by regulatory authorities (issues still to be resolved) • Other EC approvals are pending • Clinical study has initiated in the EU	• Amgen received written questions from regulators; no face-to-face or telecon meetings to discuss questions were held

Conclusions and Discussions on a Path forward in EUROPE

Amgen's Experience and Recommendations

Experience from the FDA/CID pilot programs

- Communicate – broader/deeper sharing of industry and regulator perspectives
- Collaborate – partnership in problem solving
- Converge – collective learning to reach consensus

Benefits from the US FDA CID Pilot

- Select the best trial design from multiple alternatives
- Optimize trial design features
- Improve scientific rigor and drug development efficiency
- Establish good practice for future programs
- Promote innovation and provides guidance

What should be considered for a possible CCT program in the EU?

- Resources and a plan to implement processes and systems to support a CCT pilot in the EU
- A unified, interactive, collaborative environment between sponsors and EMA including:
  - Appropriate level of multidisciplinary subject matter expertise and overall experience
  - Early dialogue between sponsors and EMA
  - Appropriate frequency of interactions between sponsor and EMA, preferably face-to-face
- A sharing of industry and regulator perspective/experience for the broader scientific community
- Agreement between sponsors and regulators on complex and innovative trial designs should result in improved efficiency in drug development (and ultimately bringing new therapies to patients who need them)

NEOS: A Complex Innovative Trial design in pediatric multiple sclerosis

Marius Thomas, Dieter Haering

Regulatory processes and systems

EMA Patients United · efpia European Federation of Pharmaceutical Industries and Associations · BARC · PPD · Norwegian Medicines Agency

Background

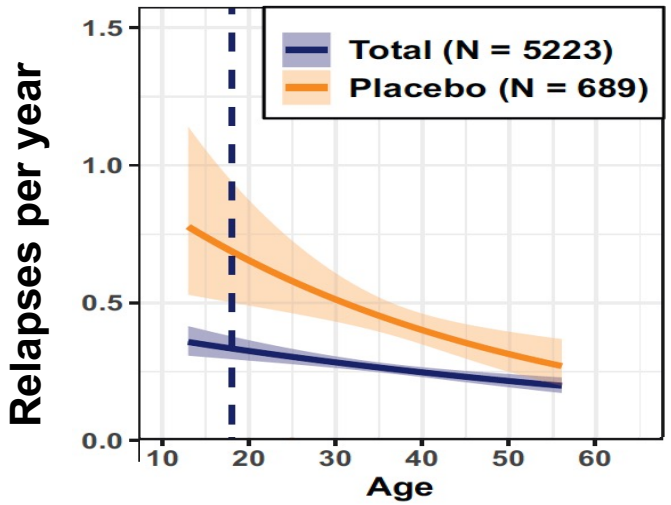
- **Pediatric MS is rare:** Only ~3-5% of MS cases start in childhood or adolescence[1,2]
- **Vulnerable population:** Children with MS show higher disease activity (2-3 time higher relapse frequency compared to adults)[3], lose brain volume from the onset (i.e. no true remission)[4], and have worse long-term prognosis, i.e. disabled at younger age[5]
- **High unmet need:** ~20 approved therapies in adults, pediatric patients only 1 approved based on randomized controlled trials in the US (Gilenya, based on only successful trial so far, PARADIGMS)

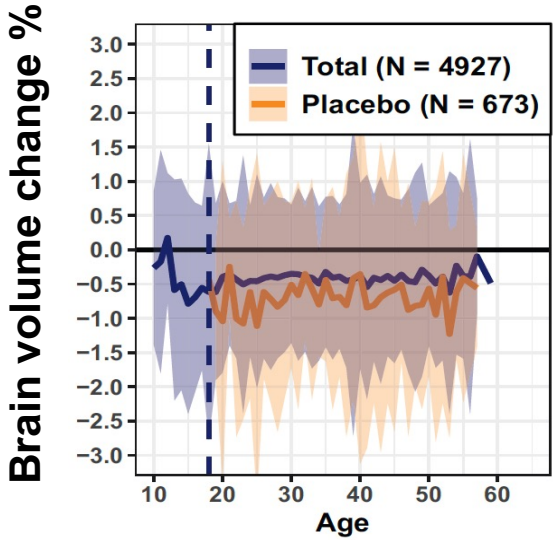
[1] Ghezzi et al. (1997) Multiple sclerosis in childhood: clinical features of 149 cases. Multiple Sclerosis Journal
[2] Chitnis T et al. (2009) Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. Multiple Sclerosis Journal
[3] Gorman et al., 2009 Increased relapse rate in pediatric-onset compared with adultonset multiple sclerosis. Arch Neurol 2009; 66: 54-9.
[4] Arnold et al., 2019 Effect of fingolimod on MRI outcomes in patients with paediatric-onset multiple sclerosis: results from the phase 3 PARADIGMS study. Neurology, Neurosurgery & Psychiatry
[5] Renoux et al. (2007) Natural history of multiple sclerosis with childhood onset. N Engl J Med 2007; 356: 2603-13.

Pediatric multiple sclerosis (MS)

Key facts

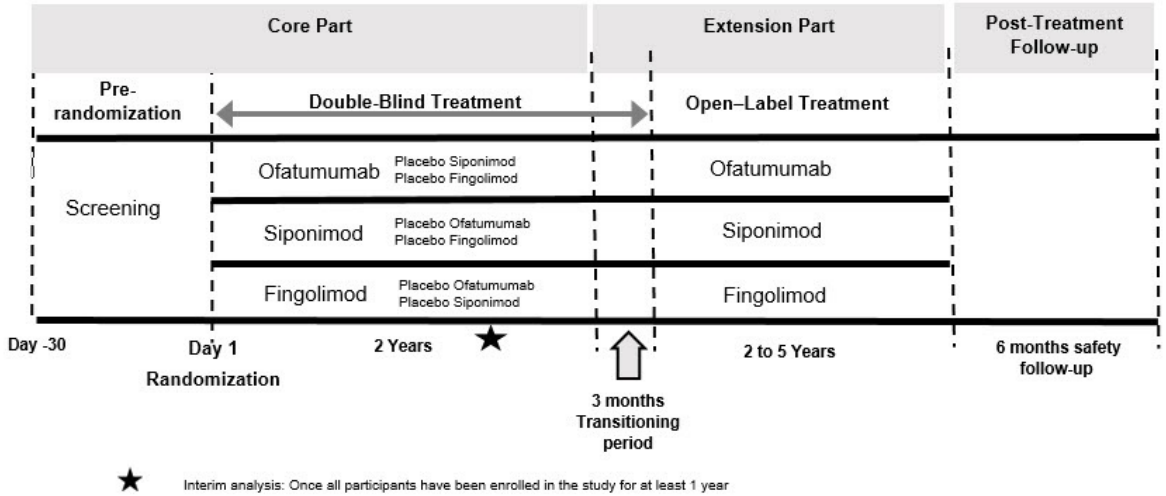
- **Biological processes involved in MS are largely shared across age span**[1]
- **Higher relapse rates** than adults but also stronger relative effect size
- Irreversible **brain volume** and **loss of neurons** from the start (=**no true remission**)





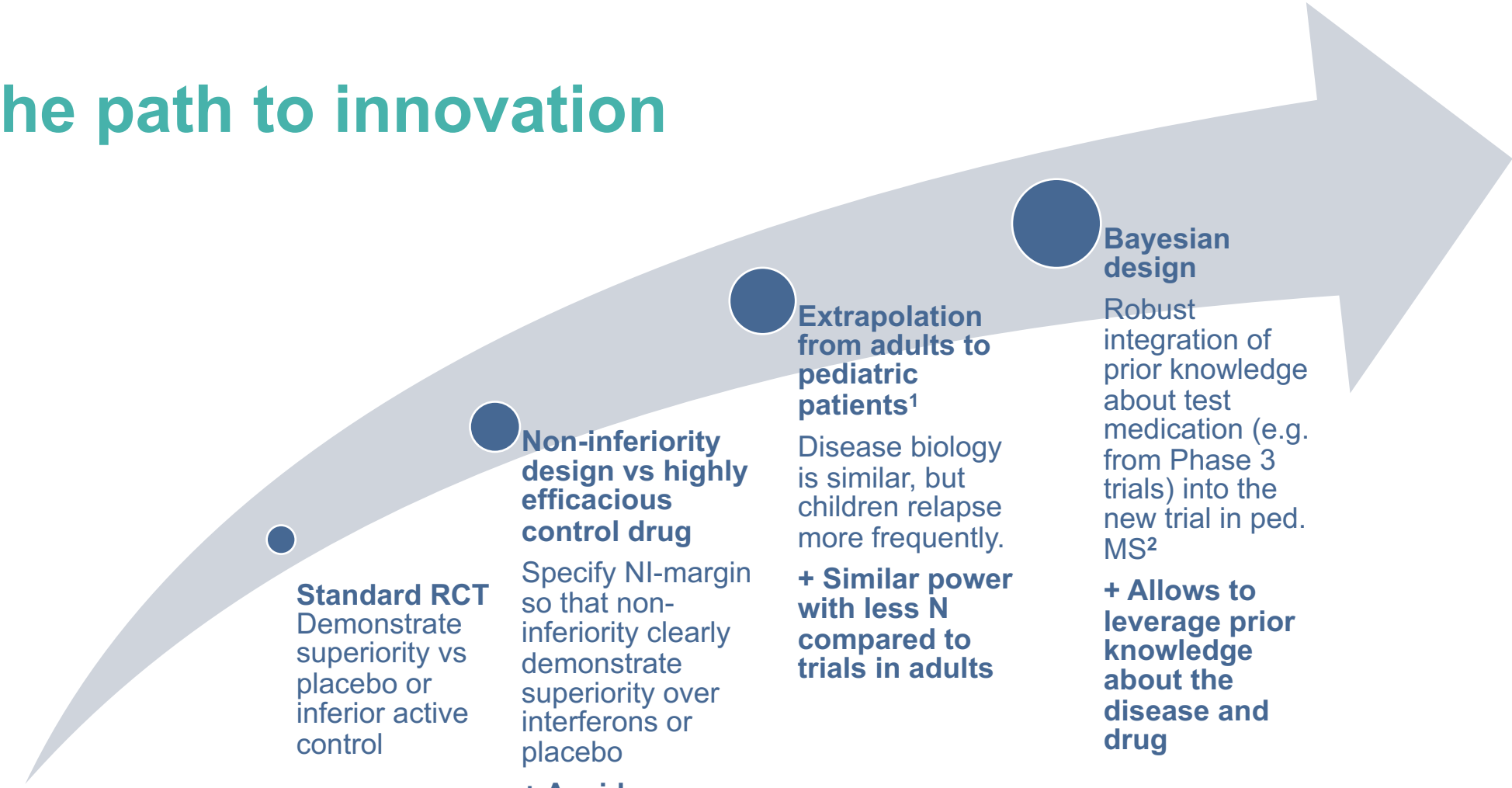
[1] Waubant et al. Neurology 2019.
Figures from Dahlke et al. (2021) Characterization of MS phenotypes across the age span. Multiple Sclerosis Journal. Total refers to active and placebo treated patients.

Agreed NEOS design:
A combined study for ofatumumab and siponimod



- **180 pediatric multiple sclerosis patients** randomized 1:1:1
- Control treatment: Fingolimod (only approved therapy in US and EU)
- **Two test treatments**: Ofatumumab and siponimod (potentially two new treatment options for pediatric MS patients)
- 2- year double-blind, triple-dummy core, up to 5 years open-label extension
- Primary endpoint annualized relapse rate
- Interim analysis after last patients has reached 1 year of exposure to allow for early stopping for efficacy

The path to innovation



Standard RCT
Demonstrate superiority vs placebo or inferior active control

Non-inferiority design vs highly efficacious control drug
Specify NI-margin so that non-inferiority clearly demonstrate superiority over interferons or placebo

+ Avoids placebo or low efficacy controls

Extrapolation from adults to pediatric patients[1]
Disease biology is similar, but children relapse more frequently.

+ Similar power with less N compared to trials in adults

Bayesian design
Robust integration of prior knowledge about test medication (e.g. from Phase 3 trials) into the new trial in ped. MS[2]

+ Allows to leverage prior knowledge about the disease and drug

[1]Schmidli et al., (2020) Beyond Randomized Clinical Trials: Use of External Controls. Clinical pharmacology & Therapeutics.
[2]Schmidli et al., (2014) Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics.

Summary of regulatory feedback: Reaching global alignment for non-standard design features can be a challenge

Topic	FDA CID discussions	EMA (PDCO and SAWP)
Extrapolation	• Concerns about extrapolation models relying on «unverifiable assumptions» • Exploration and discussion of (all) other possible prognostic or effect modifying factors required	• No specific concerns
NI-margin	• Proposed margin of 3[1] too large (some discounting is required) • Lack of pediatric data to assess between-trial variability • Systematic literature review and meta-analysis requested to have a comprehensive understanding all potentially relevant prior knowledge	• Initially proposed NI-margin of 3 was discussed as large but finally accepted for OMB PIP by PDCO based on scientific and feasibility considerations
Bayesian design	• «Bayesian framework may be useful» • Concerns about double-use of historical information in Bayesian non-inferiority design • Extensive simulations requested to understand operating characteristics under all conditions	• Bayesian design not accepted for initial OMB PIP • SAWP primarily concerned with lack of type I error control and subjectivity of weight given to historical information
Interim analysis	• An interim analysis for efficacy stopping is endorsed	• Interim analyis not accepted for initial PIP • Concerns related to inadequate assessment of long-term safety • Interim analysis not endorsed by SAWP due to adding another level of complexity to already complex design

[1] Initially sponsor proposed NI margin of 3.0 was derived based on the 95% confidence limit of the ARR-ratio between fingolimod and interferon beta-1a based in PARADIG*MS* a phase 3 trial in pediatric multiple sclerosis.

HA interactions and timelines

2017-2018

- **Initially two separate studies planned:**
  - Proposed **ofatumumab** Bayesian non-inferiority design accepted for FDA's Complex Innovative Designs (CID) Pilot program
  - Initial proposal for **siponimod** is a open-label superiority study vs interferon

2019

- **Discussions with HAs on proposed studies:**
  - Agreed PIP for ofatumumab with EMA includes non-inferiority design (NI=3.0) versus fingolimod
  - Two CID F2F meetings for ofatumumab with FDA
  - Based on HA discussion similar Bayesian non-inferiority design as for ofatumumab is proposed for siponimod

2020

- **FDA strongly encourages a combined trial, EMA concurs:**
  - Follow-up discussions with focus on Bayesian design elements with FDA
  - NEOS design (combined ofatumumab and siponimod design) accepted by US FDA
  - Discussion on NEOS design with SAWP in EU: Design and PIP modification accepted by EMA/PDCO

2021-2026

- **NEOS study:**
  - Final protocol in Jan 2021
  - Study planned to be initiated in 2021
  - LPLV planned for 2026

Key modifications on study design based on HA feedback

- Non-inferiority margin, after discounting, changed to 2.0 (instead of 3.0) with additional upper limit of the ARR (0.3) on test drugs to conclude non-inferiority vs fingolimod; as a consequence sample size increased from 50 to 60 patients per arm
- Key secondary analysis added to compare test treatments versus historical interferon data (based on a meta-analysis of historical studies)
- Ofatumumab and siponimod studies were combined into one design based on recommendation from FDA and EMA
- Tipping point sensitivity analysis prespecified to assess robustness of conclusions from Bayesian analysis under different weights to prior information; i.e. from pre-spedified weight to a «no borrowing» strategy (frequentist design)

Final study design was accepted by both FDA and EMA/PDCO

Conclusions and key learnings

- Common aim is to bring efficacious and safe treatment options to patients
- FDA's Complex Innovative Designs (CID) pilot program is a helpful initiative to develop non-standard design features collaboratively
  - Two meetings (1 hour) are short to comprehensively discuss innovative features and operating characteristics
  - Formal timelines to submit materials prior to the meeting (e.g. 90 days) give little time for updates between the two meetings
- Potential for improvement
  - Alignment between regulatory agencies (e.g. cross-agency attendance to meetings)
  - Once a sponsor is allowed to the process, opportunity for informal exchange between meetings (e.g. with an assigned primary contact familiar with the detailed proposal) would be of high value

Example of an umbrella clinical trial and its challenges

Stéphanie Kromar, EORTC Sr. Regulatory Affairs Manager

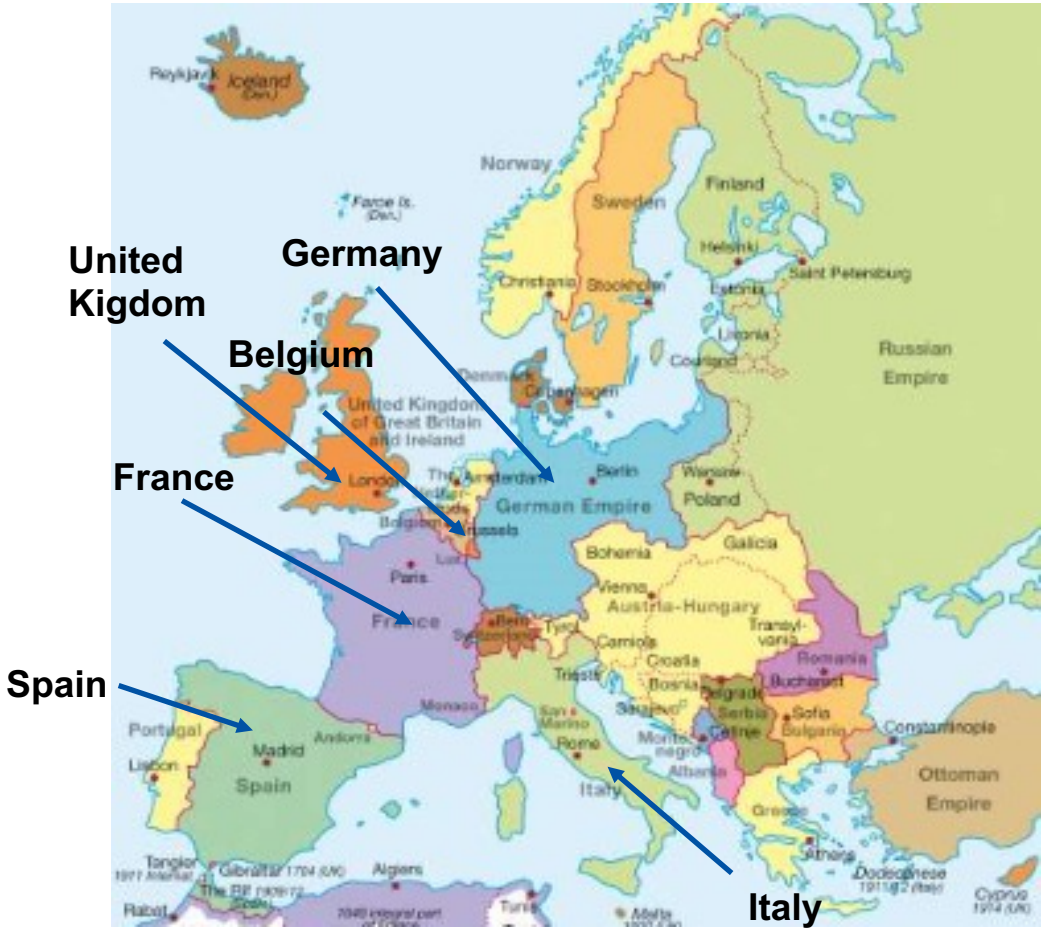
EFPIA European Federation of Pharmaceutical Industries and Associations · PPD · Norwegian Medicines Agency

Basket vs umbrella trials

Basket trial:
Groups patients whose cancers contain the same genetic change (regardless of the cancer type) and receiving all the same drug that targets this genetic change.

Umbrella trial:
Groups patients with the same cancer type, receiving different drugs matched to the genetics changes of each of their tumors.

EORTC 1559-HNCG: A pilot study of personalized biomarker based treatment strategy or immunotherapy in patients with recurrent/metastatic squamous cell carcinoma of the head and neck "UPSTREAM"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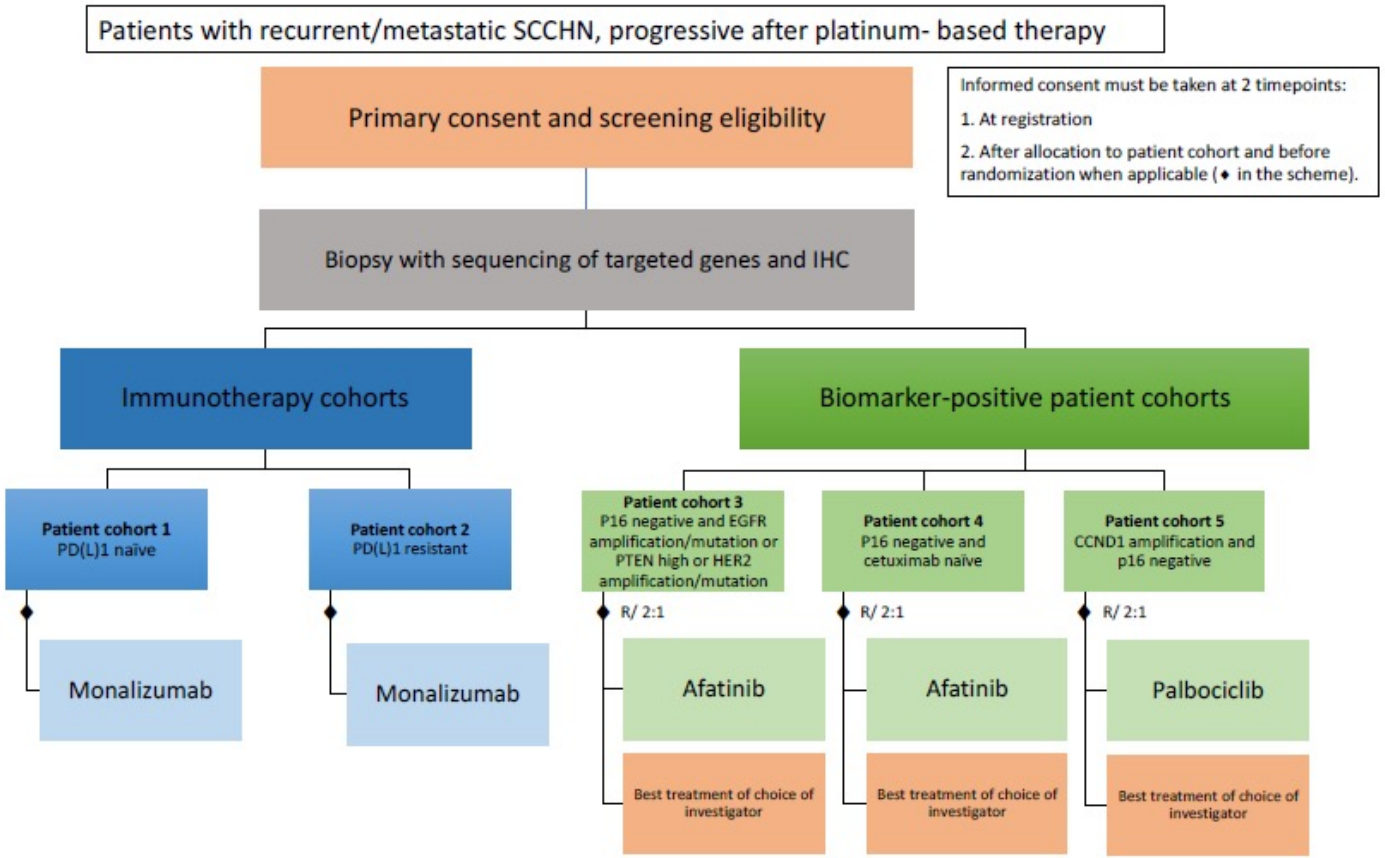
Protocol version 1.0



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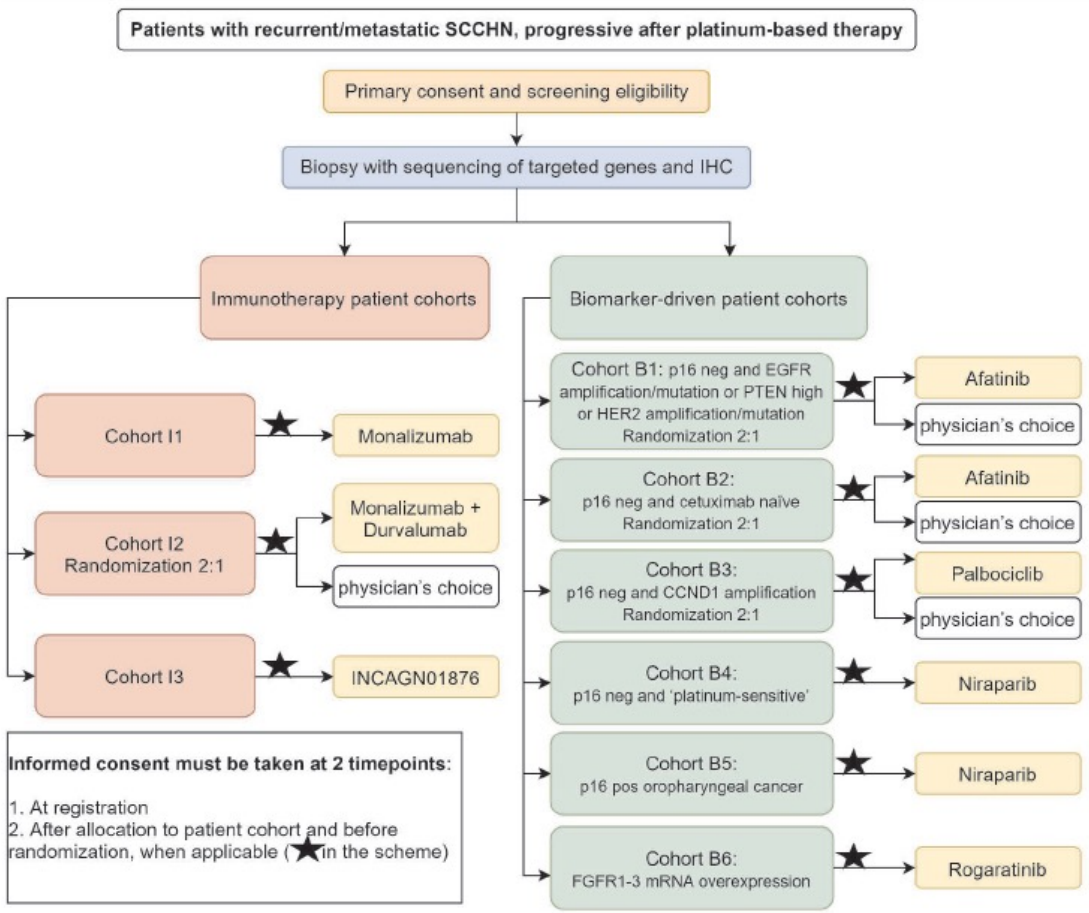
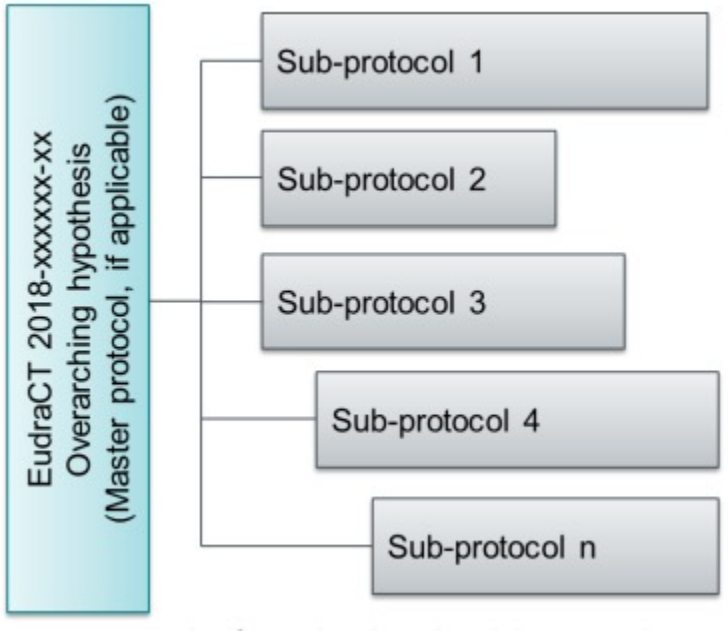
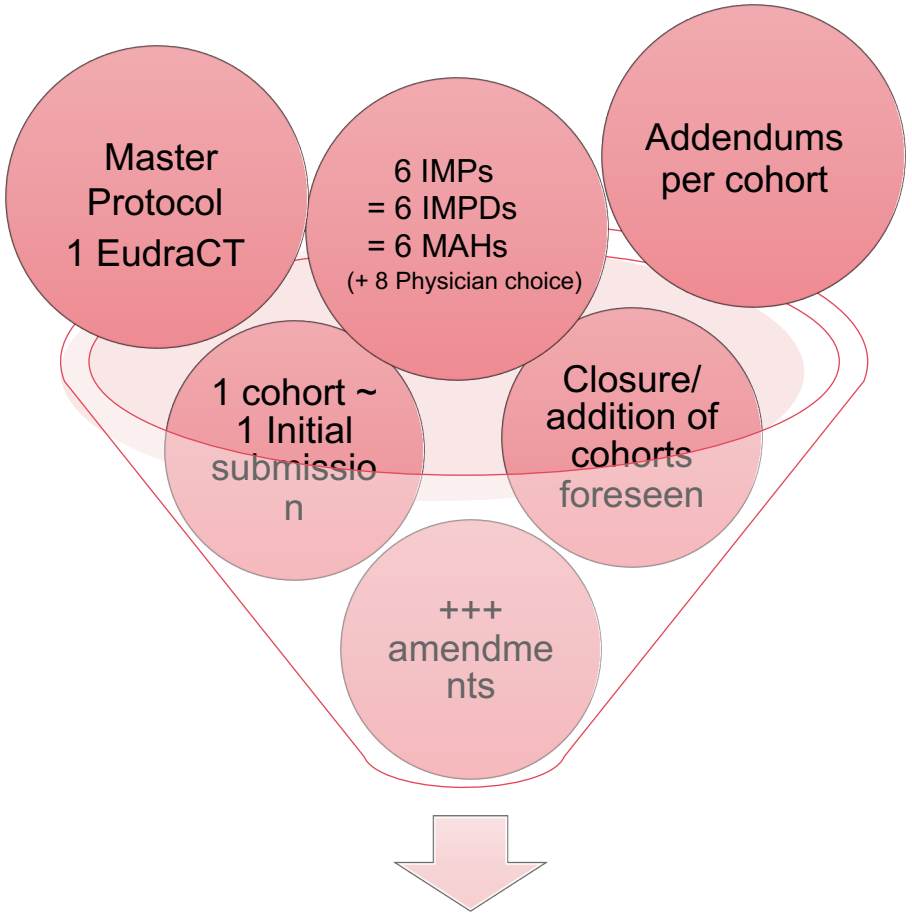


Submission strategy



Separate parts submitted as one clinical trial with sub-protocols (Source: CTFG Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials).

Challenges (1)



Difficult to handle from a Reg perspective

Challenges: famhp (2)

Conditional approval:

"The Applicant is reminded that the new cohorts to be added during the trial need to be pre-specified in the protocol according to current CTFG recommendations. This was not the case for the new cohort B6. For the next substantial amendment submission, the Applicant is requested to update the protocol with all the planned cohorts additions and to provide more specific information on the new drugs planned to be added and their number. Appropriate justification needs to be provided for each planned cohort addition. This commitment is considered as condition".

Challenges: German EC (3)

Rejection of SA:

"With the addition of the new cohort I3, a new active substance with a new mechanism of action is planned to be clinically examined. This new cohort is intended to additionally expand the previous 8-arm Umbrella study.

The addition of this new cohort I3 is a new clinical trial from a physicians and medical point of view, which must be treated as a new application and submitted as part of an AMG study. In terms of form and content, it is not a "substantial amendment" according to Section 10 GCP-VO".

Challenges: RSI (4)

- As per CTFG Q&A document – Reference Safety Information

  - ***If the RSI is within an IB which is not prepared and updated by the sponsor itself*** *(e.g. for non-commercial sponsors using a company's IB), the non commercial sponsor should have a written agreement in place with the company in which the updated approved IB is sent to the sponsor immediately. If the company has submitted a substantial amendment to authorities in EU Member States in relation to the updated IB (for any trial for which it is sponsor), the (non commercial) sponsor should await the completion of the assessment of the substantial amendment and submit the approved IB, together with any of the necessary amendments to the protocol as a substantial amendment for their own clinical trial.*

  - ***If the RSI is in section 4.8 of the SmPC*** *and this section is updated during the trial, it is recommended to submit a substantial amendment requesting approval of the update to the RSI immediately following completion of the variation procedure. Following approval of the SmPC for use as RSI in all Member States where the trial is ongoing, the updated SmPC should be used for the purposes of expedited reporting.*

    - Multiple RSIs being updated at different timepoints → difficulties in terms of compliance

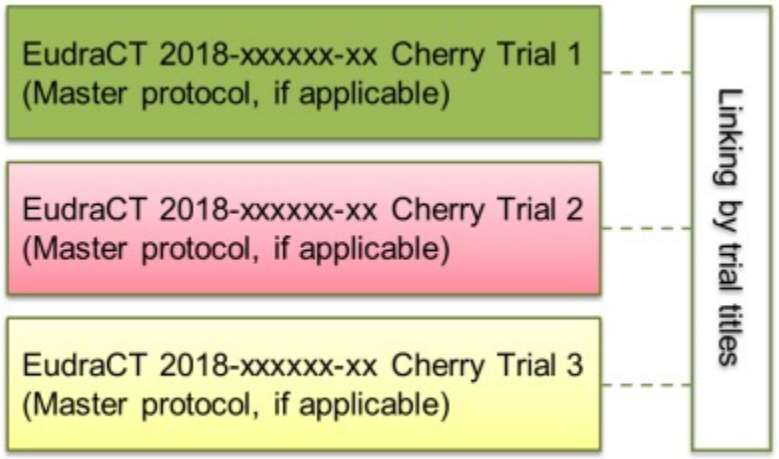
Challenges: Parallel submission of SA (5)

- We had an urgent IMPD submission while another global SA was ongoing

- We contacted authorities and they accepted parallel submissions provided that the new SA concerned a different part of the CTA

➡ Under CTR this will not be possible

If we were about to start…



The separate parts can be submitted as separate clinical trials (Source: CTFG Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials).

Thank you

Panel Discussion

Moderators

- Anja Schiel (EMA SAWP, NoMA)
- Lucia D'Apote (Amgen, EFPIA)

Panel Members

- Antony Humphreys (Head Regulatory Science Strategy Task Force, EMA)
- Elke Stahl (Chair CTFG-BfArM)
- Laurence O´Dwyer, (Chair EU-IN - HMA, HPRA
- Dionne Price (Director, Division of Biometrics IV, CDER, FDA)
- Niklas Hedberg (former Chair EUnetHTA, TLV)
- Juliana Sholter (Amgen)
- Dieter Haering/ Marius Thomas (Novartis)
- Stéphanie Kromar (EORTC)

Questions to the Panel

1. Given the unique aspects of CCT, is there a platform that is adequately agile and comprehensive enough to support a CCT pilot program in the EU?

   If the answer is no, what configuration would be necessary for such a platform?

Questions to the Panel

2. FDA has experience of an integrated platform through the CID pilot program. In your opinion, what are the key benefits for industry and other stakeholders?

Questions to the Panel

3. What can we learn from the FDA based on their experience with the CID Pilot and how can those learnings be translated into the EU regulatory framework?

Questions to the Panel

4. When should sponsors initiate engagement with regulators during the development program and what should be discussed as part of the initial interaction?

Questions to the Panel

5. How might HTAs be included in an EU CCT pilot programme?

Questions to the Panel

6. It is evident that patients need to understand the motivation of the underlying properties for a complex clinical trial design to ensure confidence in both participating in the trial, and in the end product should the medicine receive approval.

   What should the role of the patients be in the process of developing a complex clinical trial design?

   How should patients be included in the process?

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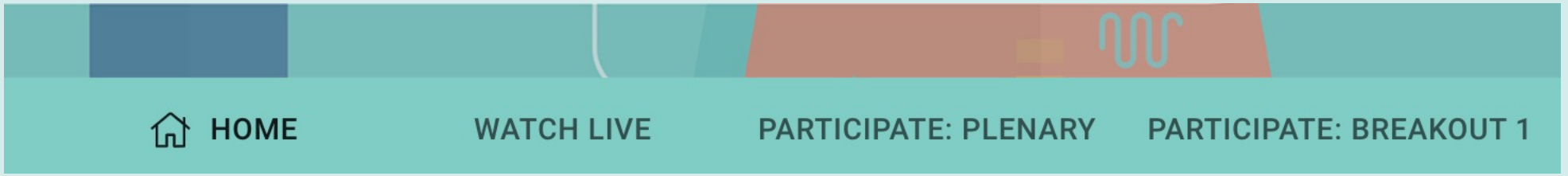

As an active participant

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