Modular Adaptive Designs

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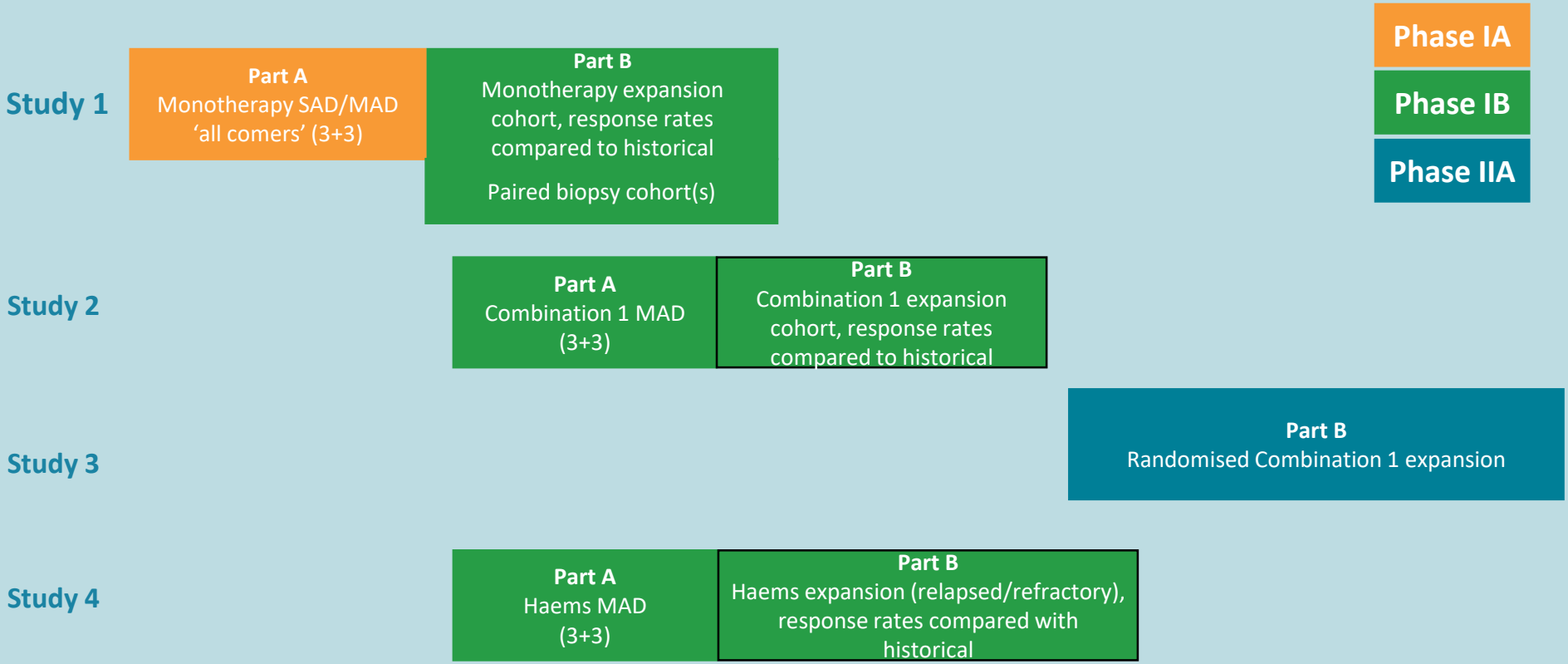
The challenges

- **Molecules with multiple hypotheses & emerging data**
  - Monotherapy
  - Chemotherapy combination
  - Novel small molecule combination(s)
  - Novel large molecule combination(s)
  - Food effect / DDI

- **Regulatory – differing requirements**
  - FDA – amend and go – risk of clinical hold
  - EU agencies – disclosure of full scope of intentions for a protocol

- **Retaining flexibility**
  - FTIP protocol language
  - Offbeat scheduling
  - Parallel cohorts / dose escalations

Traditional approach to multi-hypothesis study design



Modular protocol format

Core Clinical Study protocol

- Synopsis
- Background/rationale
- Trial design
- Overall Study Objectives
- Core Inc/Excl (Drug X related)
- Drug X relevant treatment details
- Toxicity management (Drug X related)
- AE reporting
- Data handling
- Quality management
- End of Trial
- Company/CRO contacts
- Overdose, pregnancy, maternal/paternal exposure
- Appendices

Module 1
Drug X monotherapy

- Background, objectives and rationale
- Specific eligibility criteria (incl/excl)
- Restrictions/con meds
- Module treatment (starting dose and dose escalations)
- Schedule of assessments
- Toxicity profile (AEs, DLTs)
- Assessments
- Dose modifications
- Toxicity management (monotherapy specific)
- Statistics
- References

Module 2
Drug X + combination 1

- Background, objectives and rationale
- Specific eligibility criteria (incl/excl)
- Restrictions/con meds
- Module treatment (starting dose and dose escalations)
- Schedule of assessments
- Toxicity profile (AEs, DLTs)
- Assessments
- Dose modifications
- Toxicity management (combination specific)
- Statistics
- References

Module 3
Drug X + combination 2/ Food effect/ Re-formulation

The benefits

- **One protocol responsive to emerging data**
  - Multiple combinations / monotherapy
  - Reduced time from emerging data to FSI compared with multiple studies
  - Module 2 – FDA / MHRA / ANSM – no questions

- **Core group of investigators**
  - Gain experience of emerging tox profile on one combination
  - Possible reduction in total patients exposed to novel agent

- **One team – resource efficient**
  - Single PL managing one CRO study team - multiple arms as data emerges
  - Reduction in FTE costs compared with separate studies

Key addition to protocol: adding modules in the US

Europe and Rest of World

- Company will provide a substantial amendment for review and approval

United States of America

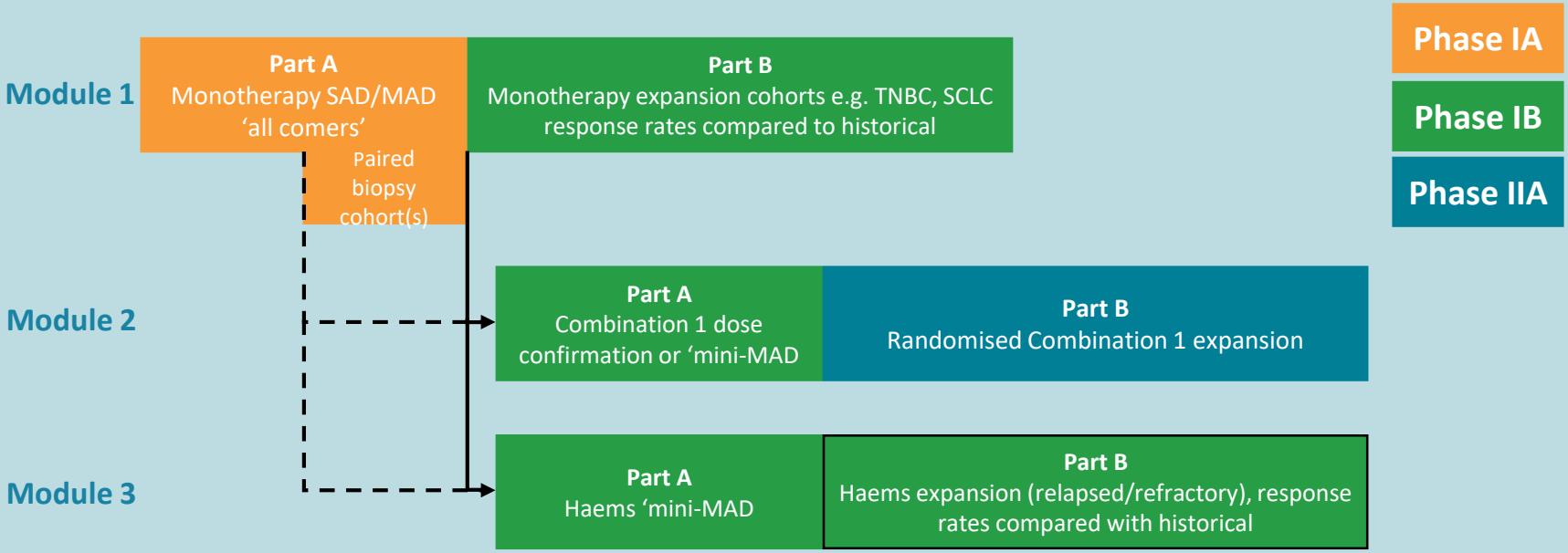
- Company will provide an amendment to the FDA 60 days in advance of planned enrolment in the cohort for any combination involving a drug for which the recommended Phase 2 dose has not been determined for the proposed dosage regimen to be employed, or at least 30 days in advance of a planned enrolment in the cohort for drugs where the recommended Phase 2 dose has been determined for the proposed dosage regime to be employed. Company will begin enrolment of patients into that cohort in the United States after FDA provide confirmations of a completed review and IRB approval

Regulatory amendment: additional modules

To support amendment of the protocol for additional modules, Company will provide a summary of all non-clinical and clinical data to support the proposed new combination and dosing schedule, this will include updating the following:

- Study objectives
- Background information providing rationale for the proposed patient population(s) and treatment plan(s)
- Study eligibility criteria
- A detailed description of the proposed study treatment plans
- A revised schedule of patient assessments
- A summary of safety data from the completed or ongoing cohort(s)/modules(s) and the proposed toxicity management plans for the proposed new combination
- A description of any dose modifications and the data (clinical safety information, clinical pharmacokinetic data, and non-clinical data) that support the safety of the proposed dose modifications for the combination/monotherapy regimen in question
- A clearly stated sample size and justification for the proposed sample size based on the objectives for that specific cohort/module
- A detailed description of the method and performance characteristics of any test that will be used to identify the patient population to be enrolled in the cohort/module, if the population will be selected based on a diagnostic assay

INDX study overview: comparison to NIH phase assignation



Study phase definitions as per 'A Handbook for Clinical Investigators Conducting Therapeutic Clinical Trials Supported by CTEP, DCTD and NCI'

Common grounds for non-acceptance (GNA) document

- **MHRA is launching the MHRA Common GNA document**
- **Common GNAs:**
  - Validation – failure to provide documents
  - Non-clinical – OECD GLP compliance, analytical methods
  - Clinical – SAE reporting, unblinding
  - Quality – retest period, MA
- **Reference safety Information (RSI) will be addressed in an upcoming update to the RSI Q&A from Clinical Trials Facilitation Group (CTFG)**
- **New Med Reg blog launched**
  - https://medregs.blog.gov.uk/