



Overview of Drug Development

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Disclaimer

The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop

Phases of Clinical Trials

Definition	Study types included
<p>Phase I Tolerability or PK as primary endpoint in the protocol, independent of the study population and secondary parameters</p>	<ul style="list-style-type: none"> ▪ Safety & Tolerability studies (Single/ multiple dose in patients or healthy volunteers) ▪ Oncology studies in patients with tolerability / MTD as primary endpoint (efficacy might be a secondary endpoint) ▪ Drug-Drug interaction & Food Effect ▪ PK in renal or hepatic impaired patients
<p>Phase IIA Exploratory (non-pivotal) study that has clinical efficacy, Pharmacodynamics or biological activity as primary endpoint, conducted in patients or healthy volunteers.</p>	<ul style="list-style-type: none"> ▪ Proof of concept, efficacy, or mechanism ▪ Mechanistic studies ▪ Dose range exploration ▪ Pilot studies
<p>Phase IIB Definite dose range finding study in patients with efficacy as primary endpoint. Exceptionally, Phase II studies can be used as pivotal trials, if the drug is intended to treat life-threatening or severely-debilitating illnesses as in oncology indications</p>	<ul style="list-style-type: none"> ▪ Definite dose finding studies ▪ Extension studies of Phase IIB studies

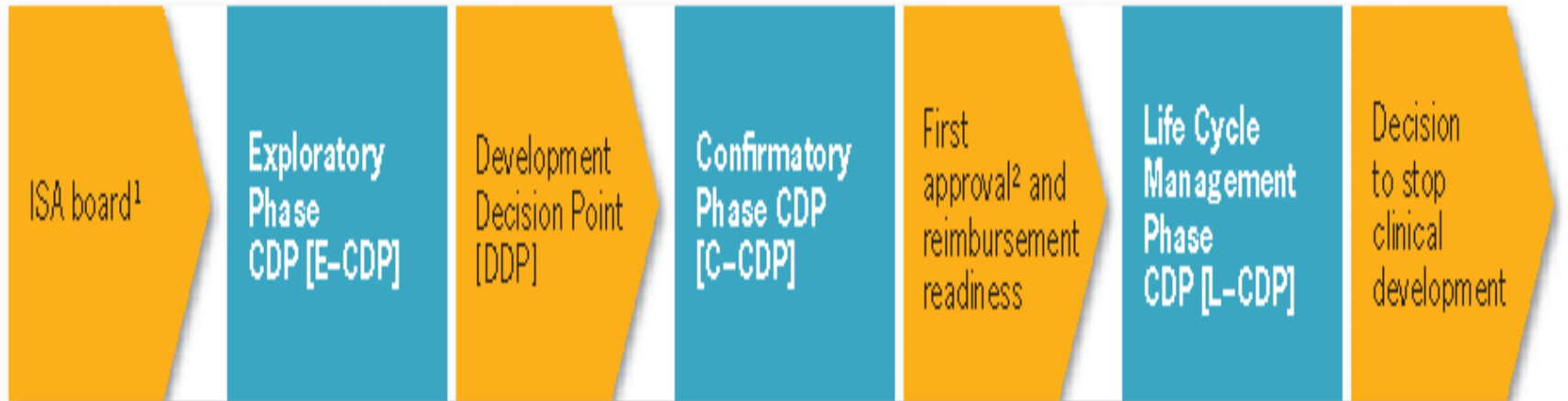
Phases of Clinical Trials

Definition	Study types included
<p>Phase IIIA</p> <p>A Pivotal* study that is a trial designed & executed to get statistically significant evidence of efficacy and safety as required by HAs for NDA / sNDA approval. It also includes studies with the aim to include claims into the label as well as Postmarketing commitments.</p>	<ul style="list-style-type: none"> ▪ Pivotal studies (vs placebo / comparator) ▪ Long term safety studies for registration ▪ Local registration studies ▪ Post marketing study commitments ▪ Phase IIIA extension studies
<p>Phase IIIB</p> <p>A study started prior to approval and whose primary intention is support of publications rather than registration or label changes.</p> <p>The results are not intended to be included in the submission dossier.</p>	<ul style="list-style-type: none"> ▪ Studies intended to support publication, claims or to prepare launch, which start before approval but are not intended for Regulatory submissions
<p>Phase IV</p> <p>A study started after approval with primary intention to support publications rather than registration or label changes</p> <p>The results are not intended to be included in a submission dossier.</p>	<ul style="list-style-type: none"> ▪ Post Marketing Surveillance studies ▪ Studies intended to support publication claims

Clinical Development Plan (CDP)

- It bridges the gap between vision and the day - to - day activities of large multidisciplinary organizations.
- The vision is transformed into distinct implementation phases and discrete steps, called clinical studies, each with well defined milestones and deliverables.

Stages of Clinical Development Plan

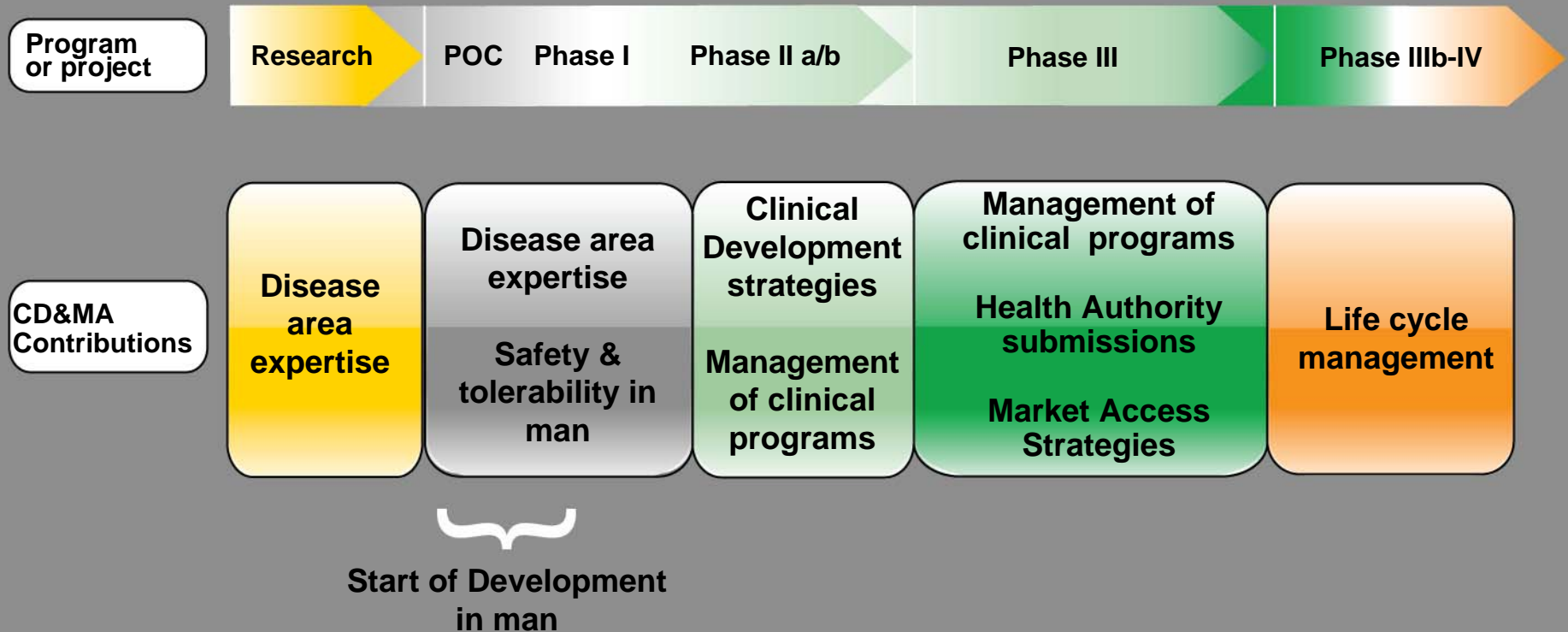


1) ISA = Integrated Safety Assessment

2) First approval typically = US or EU or J

time

Clinical Experts contribute to all Phases of Drug Development



Adaptive Designs in Clinical Development

- **Adaptive and Seamless designs** : using accumulating data to decide on how to modify aspects of the trial without undermining the validity and integrity of the trial
- **Adaptations can include**
 - Early stopping (futility, early rejection)
 - Sample size re-assessment
 - Treatment allocation ratios
 - Treatment arms (dropping, adding arms)
 - Hypotheses (Non-inferiority vs. superiority)
 - Population (inclusion / exclusion criteria; subgroups)
 - Test the statistics
 - Combine trials / treatment phases

Classical Full Development

- **Fixed Trial Designs Paradigm**, in particular for Phase III
 - Standard trial designs allow **little learning** during the conduct of the trial
 - “Established” adaptations are used in **group-sequential trials** where stopping for superiority or futility can be done according to pre-defined rules at interim analyses
 - Clearly **separated development phases** (II and III)
 - If applied to all clinical projects one **misses opportunities** for better use of information and more ethical drug development

Classical Phase III : Confirmation, Hypothesis Testing and Error Control

■ Proof of efficacy in phase III trials:

- Show that observed treatment effect is 'real' and not just random via testing of statistical hypotheses
- **Regulatory practice and guidelines (eg. ICH E9) ask that the false positive error rate is controlled for pivotal trials (usually 2.5%)**
- Trial designs, analysis and decisions rules at interim analysis **are pre-defined**
- Emphasis on trial '**integrity**' (eg regarding confidentiality of interim results)

■ Error control:

- Multiple hypothesis testing or changes of design characteristics at interim **alters the false positive error rate** of a standard statistical test

Adaptive / Seamless phase II/Phase III trial

Primary objective - to combine “treatment selection” and “confirmation” in one trial

- Enroll patients into the trial
- During the trial, select the optimal dose (or population) based on interim data
 - Based on surrogate marker, early read-out of endpoint, or primary endpoint
- Enrollment continues only on the selected dose and the comparator arm

All data from chosen arm and comparator is used in final analysis, using novel statistical methods for combining evidence from **1st and 2nd** stage to control false positive error rate and maintaining trial integrity

Comparison of ASD for treatment selection with separate phase II and III trials (1)

- Standard

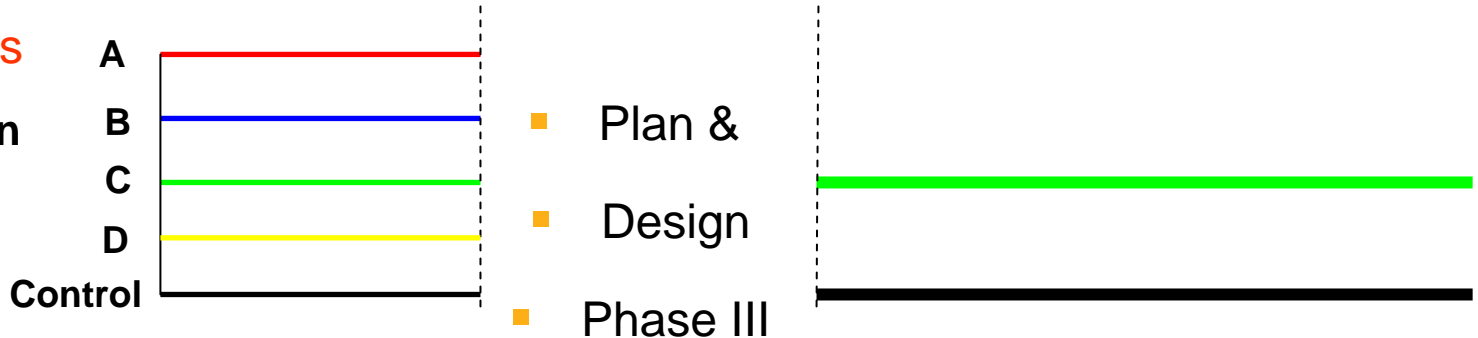
Learning

Confirming

- 2 phases

Plan & Design

Phase IIb



- Adaptive

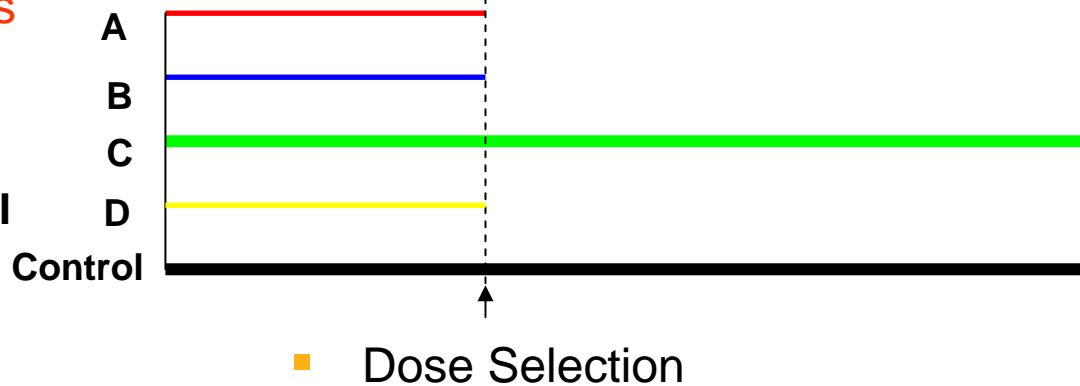
Learning, Selecting and Confirming

- Seamless

- Design

Plan & Design

Phase IIb and III



Comparison of ASD for treatment selection with separate phase II and III trials

- **Advantages of Adaptive seamless designs :**
 - Shorter overall development time → effective drugs are made available earlier for the patients
 - Increase in information value given the same number of patients
 - Long term safety available earlier (extension of Stage I patients)
- **Logistical difficulties :**
 - Number of treatment groups can change during trial → resulting implications in drug supply
 - Centers would have to be made aware of flexible sample sizes
 - Informed consent may need to be modified at interim
 - **Sufficient Health Authority interaction**
 - Careful consideration of trial integrity issues, including the interim analysis , decision process and personnel

RAD001+Femara in Advanced Breast Cancer

Motivation for adaptation

Selection of appropriate **patient sub-group** and confirmation of benefit in one seamless **phase II / III** trial

Design specifications: 2-stage seamless adaptive design

Stage 1

- sub-group selection (options: sub-group or all-patients)
- futility decision at two time points
- sub-group considered is defined upfront, based on evidence external to the trial
- Sample size could be adjusted at interim points

Stage 2

- achieve confirmation of treatment benefit while maintaining integrity of trial (false positive rate and bias are controlled)

RAD001+Femara in Advanced Breast Cancer

Adaptive trial design were reviewed by FDA and EMEA, and considered acceptable for the trial

Careful consideration and detail was required for the interim analysis and decision process

- What data will be needed to decide to adapt?
- Who will see this data, and make this decision?
- Will the results of this decision bias the trial?

Overall, a positive response

Final Remarks

- Need for **more efficient drug development process** is recognised by all stakeholders.
- Key value of adapting is not in reducing sample size, but given a constant sample size, **increase the information value**, thus making adaptive designs more ethical/efficient
- **Ethical reasons justify novel adaptive designs**, which combine learning and confirmation in one single trial while controlling the overall type I error rate
- Novartis is committed and dedicated to invest in Research & Development of ASD on a global level while being in **continuous discussions with Health Authorities**