CALIFORNIA LIFE SCIENCES

Unlocking the Path to Drug Development Success :

A Webinar for Early-Stage Biotechs

CLS Innovation & Entrepreneurship Supporting Emerging Innovators

May 14, 2024

Housekeeping

Questions

Please submit using the Q&A tool, located at the bottom of your screen.

Recording

The webinar recording will be shared with all registrants.

Resources & Materials

We will share links to all resources/materials presented today, including the deck.

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Welcome to our speakers

THOUGHT LEADERS

ALEX KAVROS, PhD
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Scientific & Regulatory Affairs
Avance Clinical

KEVIN LEACH, PhD
Senior Vice President,
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JORGEN MOULD, PhD
Senior Director,
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Alex Kavros

- Exec VP, Global Scientific & Regulatory Affairs (GSRA)
- Based in Zurich, Switzerland
- Research background in Chemistry, PDRA in CMU (PA)
- 20 years of experience in global clinical development and RA operations
  - Biotech, Pharma, Medical Devices
  - CTAs & INDs incl. EMA, SPA, Type B/C meetings, PRIME
  - Clinical studies; pragmatic, PASS and PAES
  - Marketing applications: national, MRP, ANDA & 505b2, life-cycle maintenance
  - MDs: clinical investigations and IDEs, and CE marking (Design Dossier)
  - Develop global regulatory strategies, submission campaigns and evaluate study protocols, Quality/CMC consulting in different jurisdictions
- Hobbies: reading philosophy & politics, travelling, hill-hiking and running

Jorgen Mould

- Senior Director of Scientific & Regulatory Services (GSRA)
- Based in Adelaide, South Australia
- Research background in Neuroscience (PhD), Immunology
- 25 years of experience in Drug discovery, Medical Affairs and Clinical Development
  - Academic Research, Biotech, Pharma
  - CTA/CTN submissions, Australian ethics submissions
  - Post marketing studies
  - Investigator networks/ advisory boards
  - Medical writing- Investigator Brochures, Protocols, CSRs
- Hobbies: Neuroscience, Hiking, Climbing, Photography, Nature

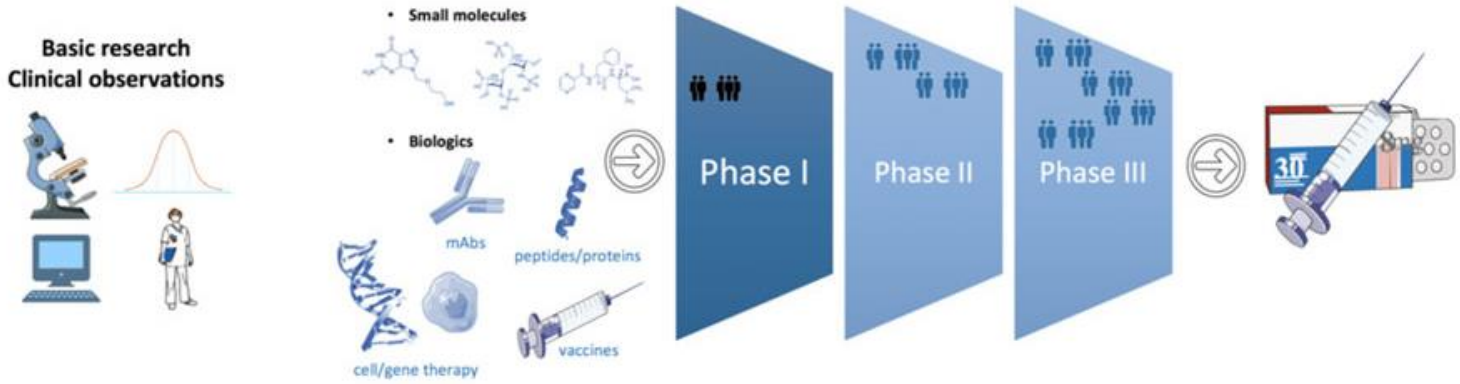
Kevin Leach

- Senior Vice President of Scientific & Regulatory Services in North America (GSRA)
- Based in Boston, Massachusetts
- Research background in Neuroscience (PhD), Immunology
- 20 years of experience in Drug discovery, Medical Affairs and Clinical Development
  - Biotech, Pharma
  - Global submissions
  - Post marketing studies
  - Investigator networks/ advisory boards
  - Medical writing- Investigator Brochures, Protocols, CSRs
- Hobbies: Golf, Tennis, Cosmology, Skiing

Drug Development: A Costly Process

- Recent estimates of the average cost of developing a new drug at $2.3 billion USD
- Generally accepted that 0.01% of all compounds make it through to market approval

Unlocking the value of your pipeline: R&D, commercial teams as well as Scientific and Regulatory, Medical Affairs, Feasibility and Clinical Operations should collaborate well before Phase 2 to keep a laser-like focus on stakeholder value.



No. of assets	**10,000**	**250**	**5**	**1**

- Safety and lack of clinical efficacy still amongst the main reasons for high attrition due to:
  - Inadequate disease target validation
  - Poor translation from animals to humans
  - Deficits in clinical trial design.
- Regulators want proof that new drugs are safer and more effective than those already on the market.
- Regulatory approval - no guarantee of success. Payors are reluctant to pay for drugs that do not deliver significant incremental benefits to patients.

Why Engage Early With a Scientific and Regulatory Services Team?

- Many biotechnology companies due to size do not have an in-house regulatory expertise or experience in clinical development
- Engagement with a scientific and regulatory consultant at an early stage in preclinical development helps to ensure that both nonclinical and clinical studies are designed in line with regulatory expectations whilst maximising return on investment
- Ideally this engagement would happen prior to IND enabling studies.

Avance Global Scientific and Regulatory Affairs (GSRA) - Our mission

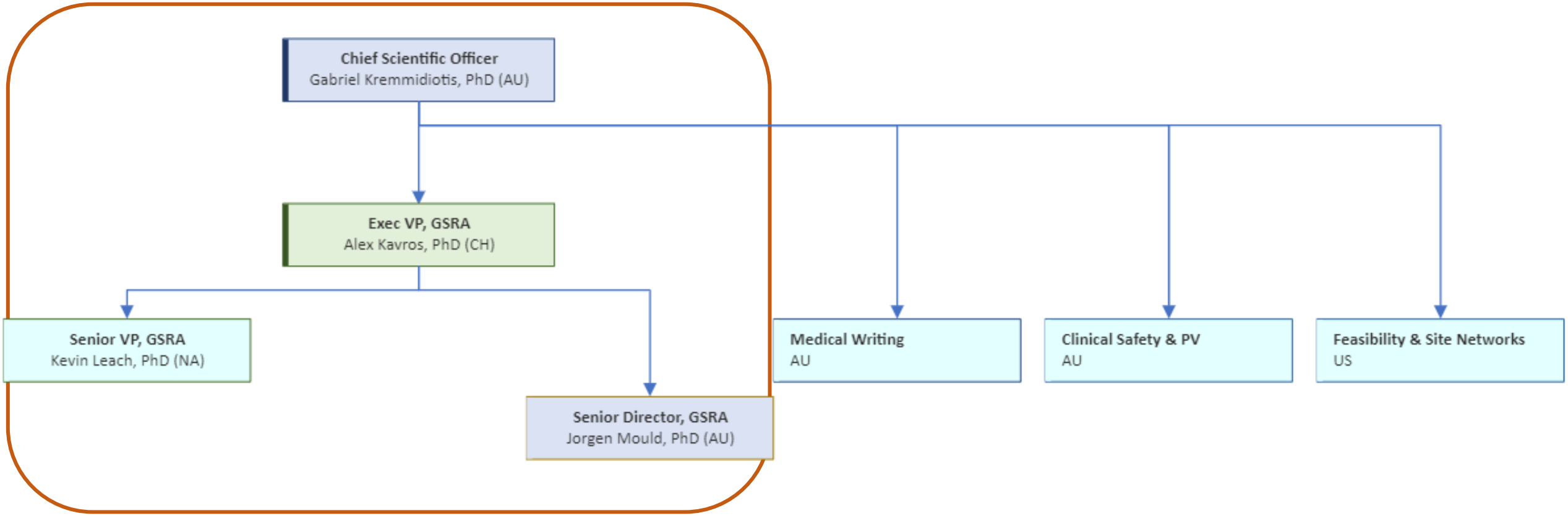
- We connect our clients to the right preclinical choices (**'ClinicReady'**) and clinical regulatory services and solutions and unleash the potential of their assets (**'GlobalReady'**).

- We act as a surrogate development department for start-up companies and assist them to demonstrate safety and preliminary clinical proof of concept of their assets.

- We offer wide-ranging regulatory consulting, intelligence and submissions management services from early to late phase of the **global clinical development continuum** and navigate our clients through regional and local regulations, directives and precedents to help them achieve their milestones.

- We ensure rigor, compliance and efficiency across all stages of drug development, trial delivery and registration planning.

GSRA Centralized (Core) Team

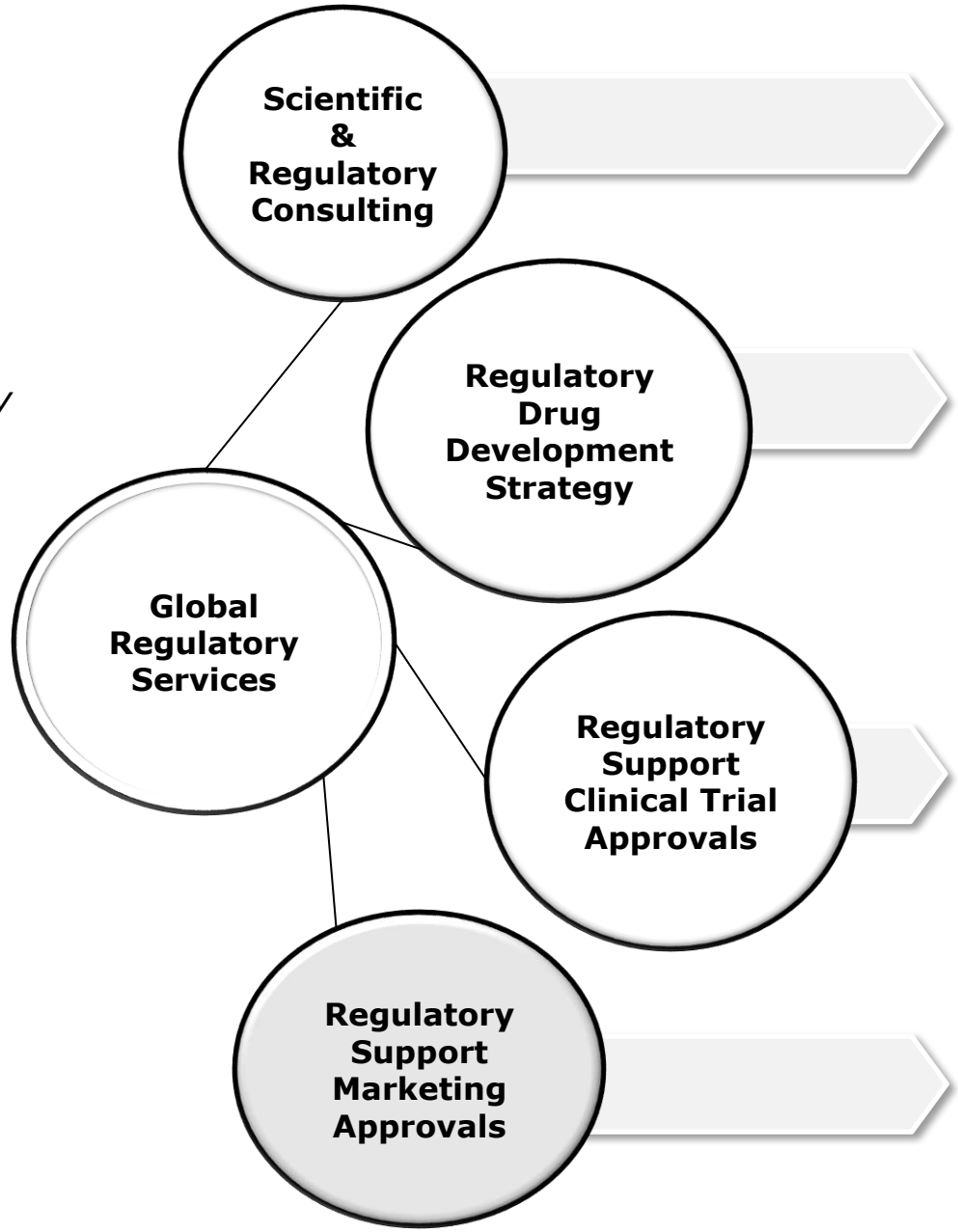


APAC: Asia Pacific
AU: Australia
CH: Switzerland
NA: North America
F&SN: Feasibility & Site Networks
SRA: Scientific & Regulatory Affairs

Scientific and Regulatory Services Offered by Avance Clinical

ClinicReady

GlobalReady



- Scientific GAP analysis & preparation of a product drug development plan
- Create or review non-clinical development plans and review Investigators Brochure
- Clinical trial designs and study protocol review

- Monitor and assess the regulatory environment in different jurisdictions, review and benchmark competitor assets and create customized regulatory summary communications
- Plan and implement strategies for successful interactions with Health Authorities
- Develop global and regional regulatory strategy and submission plans for clinical campaigns

- INDs, CTAs, updates during review, amendments/modifications
- Briefing Books, Agency Meeting Requests
- Product designation applications (Orphan Drug, Breakthrough Therapy, Fast Track, Priority Review, PRIority Medicines, Innovation Passport)
- Pediatric Investigation Plans (PIP), Pediatric Study Plans (PSP)

- Plan and implement strategies for p-NDA/BLA meetings and co-ordinate meetings
- New Drug Application (NDA; FDA).
- Biologics License Application (BLA; FDA).
- Marketing Authorization Application (MAA; EMA)
- National Regulatory Authority(NRA; TGA)

The Australian Regulatory Framework

Regulatory Framework

The Australian regulatory body for clinical trials, the Therapeutic Goods Administration ('TGA'), offers two schemes for conducting clinical trials in Australia;

- Clinical Trial Notification (CTN) Scheme
- Clinical Trial Approval (CTA) Scheme

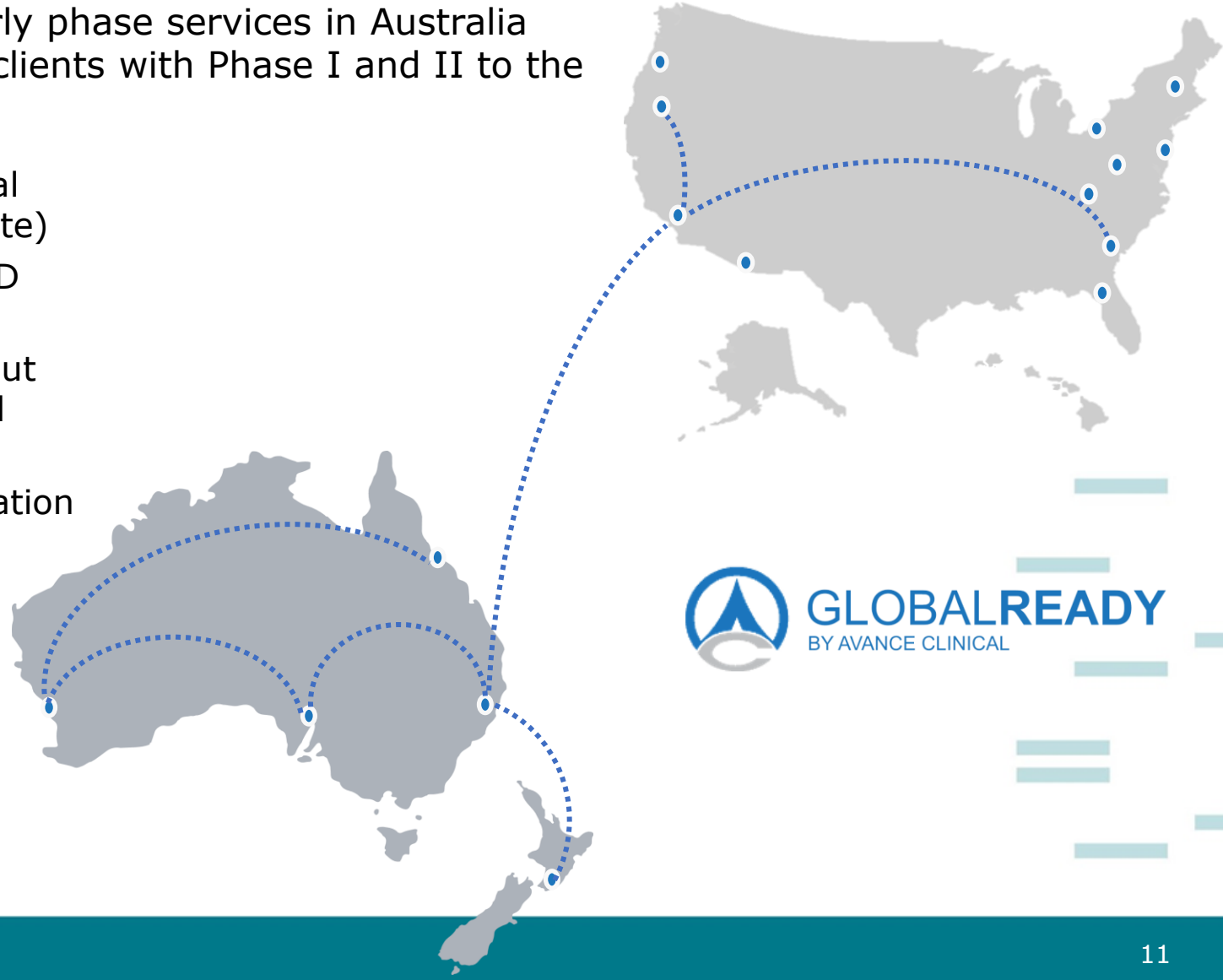
Benefits include:

- **No IND required** for clinical research trials
- Full GMP material is not mandated for Phase I clinical research trials
- Site Initiation Visit (SIV) and Study Start can be achieved in 5 – 6 weeks from ethics submission
- Government R&D grant: up to 43.5% rebate on clinical trial spend.

GlobalReady

GlobalReady by Avance Clinical delivers early phase services in Australia with a seamless transition/journey for our clients with Phase I and II to the US for later phases.

- Take advantage of the AU early phase clinical trial landscape (No IND and 43.5% tax rebate)
- Broader offering for Phase II+ trials incl. IND preparation, publishing and submission
- Transition to the US for later phases – without changing CROs (retain study knowledge and processes/team)
- Seamlessly operationalize global dose escalation and dose expansion trials across the two continents
- Harnessing significant speed and cost advantages
- FDA accepts Avance Clinical quality data – transferable and readily acceptable



GLOBALREADY
BY AVANCE CLINICAL

Broad Experience Across a Range of Investigational Products

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Product	Scope	Examples	Relevant Guidance documents
Small Molecules	Low molecular weight organic compounds < 1000 daltons	Chemicals and small synthetic peptides, oligonucleotide drugs (siRNA, ASO)	**ICHM3(R2):** Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
Biotechnology derived products and Biologics	Products derived from characterized cells through the use of a variety of expression systems including bacteria, yeast, insect, plant, and mammalian cells	Cytokines, plasminogen activators, recombinant plasma factors, growth factors, fusion proteins, enzymes, receptors, hormones, and monoclonal antibodies.	**ICHS6:** Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
Advanced therapy medicinal products (ATMP)	Cell therapies Gene Therapies Genetically modified cells	Stems cells, Differentiated mature cell products, Non-viral vectors (e.g., plasmids), Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus (AAV), retrovirus, lentivirus, poxvirus, herpes simplex virus (HSV)), Replication-competent oncolytic vectors (e.g., measles, reovirus, adenovirus, vesicular stomatitis virus, vaccinia), Microbial vectors used for gene therapy (e.g., Listeria, Salmonella, E. coli, Bacteriophage), Ex vivo genetically modified cells (e.g., CART cells)	**FDA:** Preclinical Assessment of Investigational Cellular and Gene Therapy Products **EMA:** Guideline on quality, non-clinical and clinical aspects of 4 medicinal products containing genetically modified cells **EMA:** Guideline on nonclinical studies required before the first clinical use of gene therapy medicinal products
Medical Devices	Any instrument, apparatus, appliance, software, implant, reagent, material used alone or in combination for diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease;	"Range from simple tongue depressors and bedpans to complex programmable pacemakers, and closed loop artificial pancreas systems. Additionally, medical devices include in vitro diagnostic (IVD) products, such as reagents, test kits, and blood glucose meters"	**ISO10993-1:2018:** Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process

Typical Non-Clinical Studies Required for Advanced Therapies

The standard elements of non-clinical development have to be fit for purpose and often take a case-by-case approach

- Cell and Gene Therapies

Biodistribution

Standard list of tissues

- Informed by historical data relevant to the therapy e.g., AAV serotypes have a known tropism
- Pharmacology endpoints can be added
- Multiple dose levels including highest dose in tox study
- Two time points – time of maximal expression and a late time point to indicate persistence
- Data can be used to inform the need for DART studies – if there is distribution to germline cells.

Duration of Toxicology Studies

- Based on therapy characteristics
  - persistence, expression profile of the transgene, if clonal expansion is possible
  - informed by the biodistribution study
- Example: many AAV therapies reach steady state expression in 4 weeks and as such a 13-week tox study has been used.

Species Selection

Translatability in terms of

- Tissue uptake of the therapy and the pharmacologic activity of the transgene
- Consider the impact of previous virus exposure to the animals on immunity to the therapy
- Adaptive humoral responses could lead to a neutralizing or cell mediated toxicity that would not be relevant to humans
- Single species/hybrid pharmacology/tox can be acceptable.

Genotoxicity

- Insertional mutagenesis
- Off target gene editing
  - Ex vivo editing – karyotyping
  - Bioinformatics to assess risk
- Traditional Gene tox only for novel impurities or components that are consistent with the standard battery of assays (lipid components).

Common Questions From Sponsors Regarding What is Needed for Approval to Conduct Clinical Trials in Australia

Q: What nonclinical studies do I need prior to conducting FIH studies?
A: Australia follows ICH guidelines e.g. (ICHM3(R2), ICHS3, ICHS6, ICHS7A, ICHS9) and the same nonclinical studies that would be conducted prior to an IND submission would be expected as appropriate for the product type, route of administration, therapeutic indication and planned FIH study

Q: Do safety/toxicology studies need to be GLP?
A: As per ICH guidance, all pivotal safety/toxicology studies are expected to be GLP compliant

Q: Do I need to submit nonclinical safety/toxicology reports as part of the approval process?
A: In general, and for CTN submissions, ethics will rely on all relevant supportive nonclinical (and if available clinical data) to be provided in the Investigators Brochure.

Q: Does the Investigational product need to be manufactured GMP and how much stability data will I need?
A: The TGA has adopted version PE009-15 of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products (PIC/S Guide to GMP), excluding Annexes 4, 5 and 14, as the manufacturing principles for medicines and active pharmaceutical ingredients. Manufacture for Phase 1 studies in Australia is not subject to inspection and licensing by the TGA. It is expected however that products are manufactured according to GMP principles.

Unlocking Your Pipeline

Understand what outcomes matter to patients and other stakeholders – patient is in focus

- Identify patient needs not yet met by competitors for specific indications, based on RWE and Natural History Studies
- Understand the profile a new compound should have to satisfy those needs
- Identify a sub-set of patients who might benefit
- Segmentation restricts the size of the market, but it accentuates the potential differentiation from competitors' compounds
- Focus to other health care stakeholders - governments, regulators, HTAs and payors; their influence on licensure and pricing varies by geography
  - Regulators are concerned about the risks and benefits compared with SoC and mostly require RCTs and "hard" clinical endpoints directly related to the progression of the disease
  - Payors care about the total cost impact on their patient population
  - HTAs want to know whether the incremental benefits of a new drug can justify its costs
- Find an approach that satisfies FDA and EMA, PMDA and NMPA

Target product profile (TPP)

- To be differentiated from the future SoC at the time of launch; delivers max. value to stakeholders and carries an acceptable risk profile in terms of development risk
- Even before PoC, a plan is needed that maximizes a drug's potential value, taking into account all the possible indications and respective patient segments.

Unlocking Your Pipeline

Sharpen the focus of phase 2 to define value as well as dose

- To identify the sub-set of patients who have the optimal risk-benefit profile for the compound
- To start testing additional questions likely to be raised in phase 3 by stakeholders
- Seek input by payors, HTAs and advisory boards on what a new compound might have to deliver to be judged better than the standard of care; which end-points need to be proven; and the data required
- Comparative studies that give an early sense of how the compound differs from the SoC and how pivotal studies may need to be refined are also useful
- Should be designed to optimize costs, time and data quality but without sacrificing ethical standards
  - Example: a compound addressing an already validated mechanism. Time and costs efficiencies by using **adaptive design** that combines phase 2a (PoE) with 2b (dose ranging), thereby reducing start-up times and improving dose-response estimates.

When entering phase 2, a development strategy for a MoA that addresses more than one indication is needed (staggered development using basket trials).

Use of Master Protocol Design in Early Phase Development

- It is crucial to have validated biomarker assays with strong analytic performance in a clinical setting, since an assay with low specificity will dilute the treatment effect in enrichment designs and an assay with low sensitivity for resistance variants also dilutes treatment effect
- Defined process for situation of patient allocation in the case of two or more positive biomarkers (e.g., in umbrella trials)
- Clarify reporting responsibilities and procedures for safety oversight for trials with multiple IMP suppliers
- Agencies are more likely to approve complex and innovative designs for exploratory trials as there is general concern that these studies can be susceptible to bias.
- Description of type I error control in trial protocol
- Prospective planning of any adaptive design in the protocol is essential for Regulatory approval and to avoid bias and keep the trial integrity
- Adaptations regarded as acceptable if they are based on prospectively planned blinded interim analyses and an independent DMC: - eligibility criteria, - sample size, - secondary endpoints without an association with efficacy parameters, - group sequential plans and futility, - data analysis plan
- Assessment of potential multiplicity issues deriving from complex trial design with each planned and new adaption and provision of mitigation strategies in the protocol (and amendments) to avoid multiplicity issues
- Agencies and IRBs/ECs have concerns they may not receive sufficient information on safety data for evaluation before next “phase” or arm of a trial is opened.

Innovative Designs in Early Phase

Regulatory approved products that include some adaptive design element in their clinical development

Compound	Adaptive design element	Key Results/ outcome	Indication in EU label	Indication in US label
			at least partially supported by data generated via adaptive clinical designs	
Symtuza (EU/USA) Janssen-Cilag International N.V.	Phase I, relative bioavailability, adaptive-design, randomised, open-label, multiple-dose, 3-part, multiple cohort. Compared three formulations of fixed dose combination (monolayer vs bilayer; 25 mg vs 10 mg of one active ingredient) repeated dosing. Aim was to select one formulation for Part 3 of the study and for further development, starting with a Phase 2 study. Part 3 evaluated possible interaction of certain combinations. n =102	Formulation 3 was chosen for Part 3 of the study and for further development	Symtuza is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg). Genotypic testing should guide the use of Symtuza (see sections 4.2, 4.4, and 5.1). Symtuza : EPAR - Public assessment report https://www.ema.europa.eu/en/documents/product-information/symtuza-epar-product-information_en.pdf	SYMTUZA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults: • who have no prior antiretroviral treatment history or • who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir. SYMTUZA prescribing information

Innovative Designs in Early Phase

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Regulatory approved products that include some adaptive design element in their clinical development

Compound	Adaptive design element	Key Results/ outcome	Indication in EU label at least partially supported by data generated via adaptive clinical designs	Indication in US label at least partially supported by data generated via adaptive clinical designs
Lucentis Ranibizumab Novartis Europharm Limited (extension of indication)	Phase II: Originally flexible design. Based on outcome of interim analysis, there were two parts for analysis of efficacy, a pilot/supportive part (n=42) and a confirmatory part (n=109) with the new primary efficacy endpoint 'mean average change in visual acuity from baseline from Month 1 to Month 12'	Sufficient data support the choice of dose, 0.5 mg, the flexible dosing frequency, the re-treatment and stopping criteria that are based on assessment of VA. A statistically convincing effect of ranibizumab in the treatment of visual impairment due to DME has been demonstrated	Lucentis is indicated in adults for: • The treatment of neovascular (wet) age-related macular degeneration (AMD) • The treatment of visual impairment due to diabetic macular oedema (DME) • The treatment of proliferative diabetic retinopathy (PDR) • The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) • The treatment of visual impairment due to choroidal neovascularisation (CNV) https://www.ema.europa.eu/en/documents/variation-report/lucentis-h-c-715-ii-0020-epar-assessment-report-variation_en.pdf https://www.ema.europa.eu/en/documents/product-information/lucentis-epar-product-information_en.pdf	LUCENTIS is indicated for the treatment of patients with: 1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD) 1.2 Macular Edema Following Retinal Vein Occlusion (RVO) 1.3 Diabetic Macular Edema (DME) 1.4 Diabetic Retinopathy (DR) 1.5 Myopic Choroidal Neovascularization (mCNV) LUCENTIS prescribing information

IND/CTA Review: Regulators' FAQs

Avance's Experience - Clinical Study Protocol

Study Protocol Topic	Issue / FAQ by HAs and IRBs/ECs	Remedy
Starting dose	**Lack of calculated safety margins** based on (free) exposure (AUC, Cmax) at the NOAEL in the animals to the expected exposure in the intended clinical trial. • For early phases, check NOEAL or MABEL and ensure that selected dose is acc. to defined NOEL/NOEAL/MABEL • For later studies, check previous studies, ensure dose selection is based on available data.	a. NOAEL is accepted benchmark for safety when derived from appropriate animal studies and serves as the starting point for determining a safe starting dose. Estimation should be based on state-of-the-art modelling (e.g. PK/PD and PBPK). **HED = animal dose (NOAEL) in mg/kg x (animal weight in kg/human weight in kg)$^{0.33}$** b. Exposure showing PD effects in the non-clinical pharmacology studies, including ex vivo and in vitro studies in human tissues if feasible, should be determined and these data used to determine MABEL in humans and an estimation of the pharmacologically active dose (PAD) and/or anticipated therapeutic dose range (ATD) in humans.
Dose escalation and max. exposure	For dose finding studies (ICHE4): • Ensure max dose is according to animal data (PK, $t_{1/2}$) • **Are there rules about dose escalation steps?** • Check with previous studies or comparable products • Check whether PK profiles and PD effects indicate plasma levels of IMP are not maintained throughout the entire dosing interval; a different dosing interval/regimen can be proposed (e.g. from BID to QID)	Criteria for dose increases incl. stopping rules during a CT, should be outlined The maximum increase in dose/exposure from one cohort to the next, as well as a maximum number of cohorts to be evaluated, should be stated in the protocol. The choice of the dose levels should include an estimate of exposure levels to be achieved and potential adverse effects (if any).

IND/CTA Review: Regulators' FAQs

Avance's Experience - Clinical Study Protocol

Study Protocol Topic	Issue / FAQ by HAs and IRBs/ECs	Remedy
Duration of treatment	1. Is the **duration of treatment sufficient to observe a meaningful output?** 2. In accordance with DoH the study protocol should contain information about provision of treatment after the end of trial to patients who are deriving clinical benefits from the IMP	A duration of treatment of 'until commercially available/marketing authorization' and/or 'administration of the IMP until commercially available/MA' cannot be considered a valid study objective/endpoint in an initial CTA application, in an extension phase of an ongoing trial or in an extension trial
Precautions to apply between treating subjects within a cohort (both between subjects and cohorts)		In early phase studies, use the Sentinel approach (dose patients one after the other in the beginning) If adults and adolescents in the study, start with adults and assess safety
Precautions to apply between cohorts (e.g. from adults to adolescents)	Is a DSMB necessary/used?	If adults and adolescents in the study, start with adults and assess safety
Dose stopping criteria	Is there a **section on dose stopping criteria in protocol**? Is the stopping rule the end of the study for the patient or a temporary hold? In FIH trials where no information is available about the safety profile of the IMP and/or HV trials where the trial participants do not derive any benefit from trial participation, absolute dose escalation stopping criteria should be defined to protect participants' safety.	In FIH trials and HVs trials where no benefit from participation is derived (suggested text): In case of occurrence of an SAE considered to be at least possibly related to the IMP or in case of two severe or clinically significant AEs considered to be at least possibly related to the IMP, dosing will be stopped, and the trial will be halted.

IND/CTA Review: Regulators' FAQs

Avance's Experience - Clinical Study Protocol

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Study Protocol Topic	Issue / FAQ by HAs and IRBs/ECs	Remedy
Communication plan/system in to ensure prompt communication of safety concerns among all the participating sites	**Lack of a system ensuring prompt communication of safety concerns** among all the participating sites.	A detailed co-ordination and communication plan must be provided in the protocol, including how the assignment of patients to a cohort will be undertaken, in view of small cohort sizes and in cases where multiple international sites are involved (sentinel approach). This plan should also address dissemination of safety data to all sites, and how this will be handled.
AE and SAE recording	**No additional recording period for safety is foreseen in Schedule of Events** - Recording of AEs and SAEs must start after the trial participant signs the ICF and must be performed at least until the end of the systemic exposure to the IMP (five elimination half-lives). - If disease progression (DP) is a trial endpoint the protocol must ensure periodic review of disease progression cases in order to identify potential IMP-induced increase of disease progression.	Explanation is required A written rationale should be provided in case this is not applicable. The protocol must not automatically exempt DP events from reporting requirements. Provisions for recording DP as an adverse reaction/serious adverse reaction should be in place if DP is deemed related to IMP by the investigator.
Contraceptive requirements	Example: **Lack of a clear definition of abstinence**	https://www.hma.eu/fileadmin/dateien/HMA_joint/00-_About_HMA/03-Working_Groups/CTCG/2024_HMA_CTCG_Contraception_guidance_Version_1.2__March_2024.pdf
Unblinding in case of clinical emergency	**Sponsor cannot require or insist on being involved in the decision to unblind**, stall or delay in any way the unblinding of trial subject treatment in emergency situations.	A phrase requesting to contact the medical monitor before unblinding should not be part of the protocol. The responsibility to break the treatment code in emergency situations resides solely with the investigator

Selected US FDA Regulatory Designations For Expedited Review

- **Orphan**
- **Rare Disease Endpoint Advancement**
- **Breakthrough**
- **Pre-IND Meetings**

Orphan Drug Designation

- A rare disease is one with less than 200,000 patients
  - In the USA- >7000 rare diseases, affect 25-30 million Americans
  - >6000 designations have been granted, in >1000 different diseases
    - >1000 approvals
- Benefits
  - Tax credit of 25% of clinical R&D costs
  - No submission costs
  - Prolonged market exclusivity
  - Orphan drugs are eligible for closer collaboration with the FDA and
    - In rare diseases the FDA encourages the use of "innovative clinical trial methods such as adaptive and seamless trial designs, modeling and simulations, and basket and umbrella trials"
- Can be obtained after a molecule shows activity in a relevant biological model
- If for a pediatric population a PRV can be granted.

Rare Disease Endpoint Advancement Pilot Program

To support novel endpoint efficacy development for drugs that treat rare diseases.

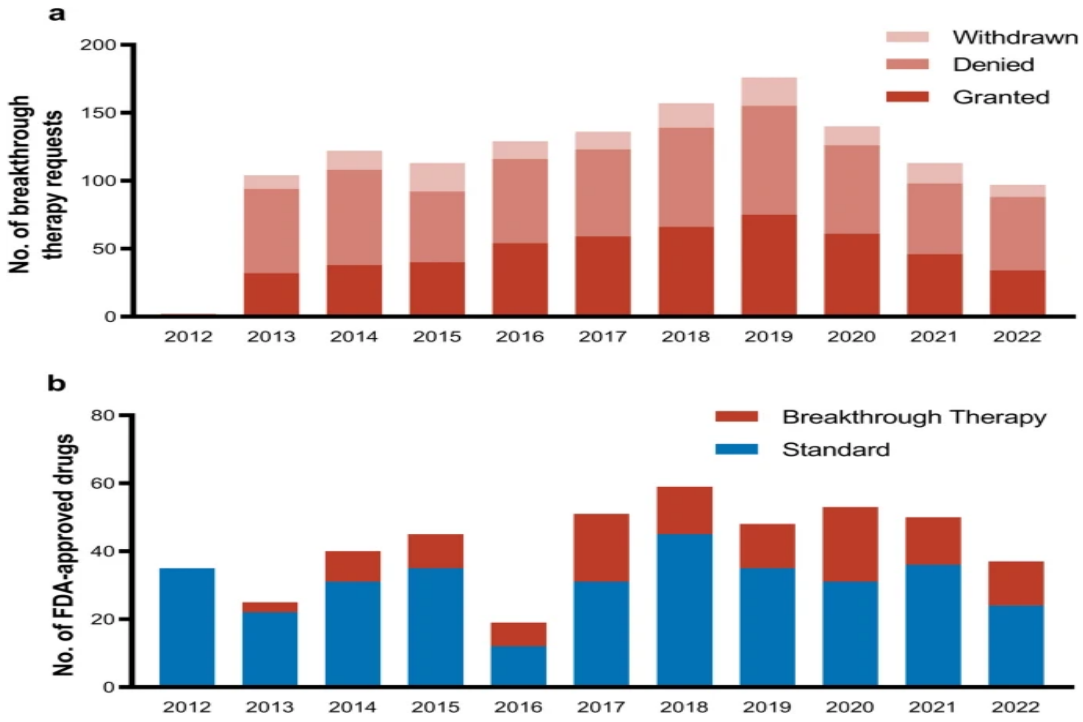
- Eligibility
  - Sponsor has an active pre-IND or IND for a rare disease
  - Exceptions
    - Sponsors who do not yet have an active development program but have, or are initiating, a natural history study where the proposed endpoint is intended to be studied are also eligible.
    - The FDA may also consider accepting a proposal for a development program for a common disease that includes innovative or novel endpoint elements, including the specific endpoint and/or the methodology being developed, if there is sufficient justification that the proposal could be applicable to a rare disease
- Looking for endpoints that-
  - Have the potential to impact drug development more broadly, such as one that uses a novel approach to develop an efficacy endpoint or an endpoint that could potentially be relevant to other diseases.
  - For surrogate endpoints, those that use novel approaches for collecting additional clinical data in the pre-market stage to advance the validation of these endpoints.
    - If the sponsor is proposing to develop a surrogate endpoint as part of a rare disease application, participation in a prior Type C Surrogate Endpoint meeting is encouraged.

Breakthrough Therapy Designation

- Expedite the development and review of drugs with a preliminary large benefit in treating a serious or life-threatening disease
- In response to the perceived value of new molecular platforms like gene and cell therapies, precision medicine and argued that these new drugs were so effective that waiting for the completion of Ph3 trials would be like withholding therapy from patients who needed it
- Sponsor gets, early and often meetings with the FDA (pre ph1) with more senior leaders at FDA
- Receive all of the Fast Track benefits
- Can use a surrogate endpoint
- Is usually requested after proof of concept and before the beginning of the first pivotal trial
- FDA gives feedback on breakthrough designation within 60 days

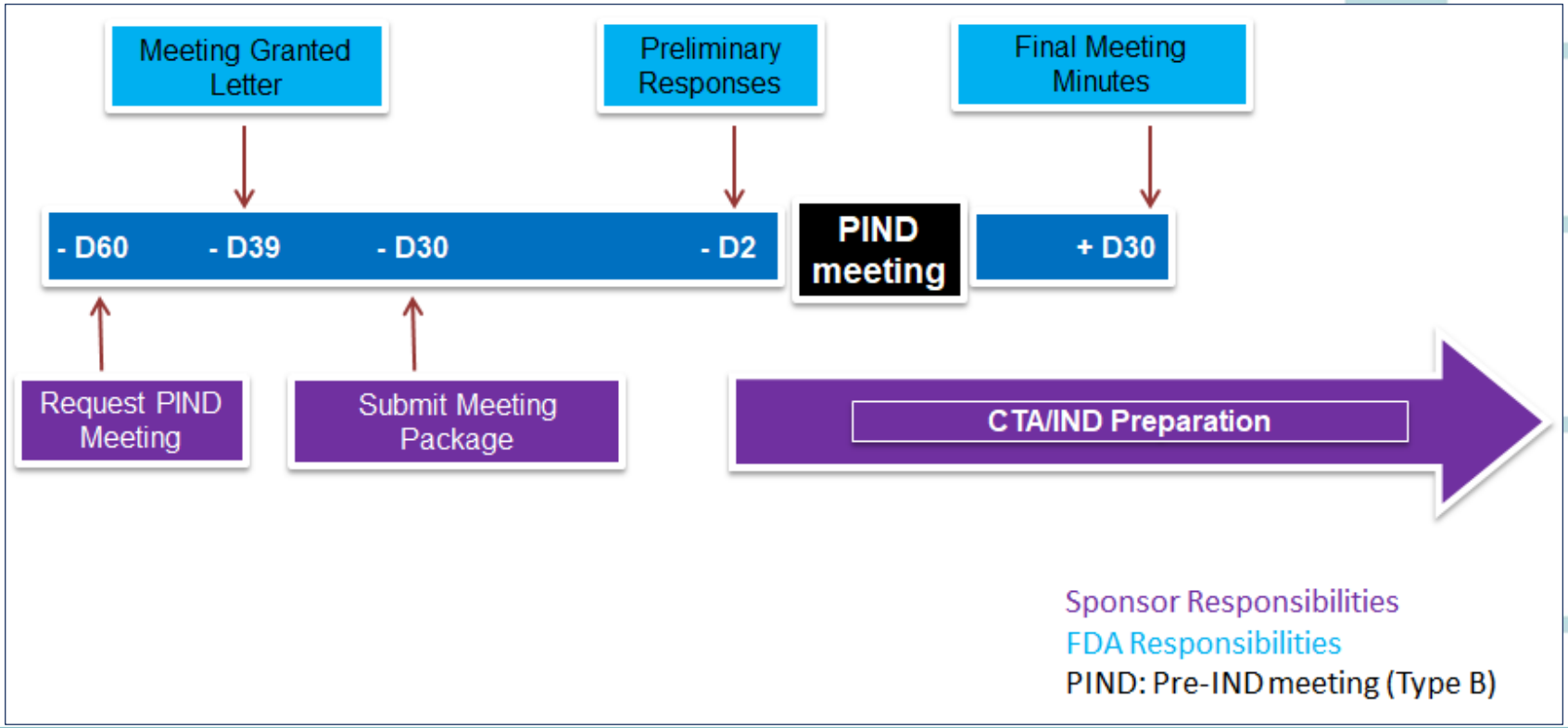
Breakthrough Designation

- Until the end of 2022, the FDA received a total of 1,289 breakthrough therapy requests
- 506 (39%) were granted
- This led to the approval of 125 new breakthrough-designated drugs



Pre-IND Meetings

- To help sponsors prepare to submit a complete investigational new drug application
- To ask questions about adequacy of the non-clinical program
  - Toxicology
  - CMC
- To ask questions about design of proposed clinical program
  - Proposed starting dose
  - Dose escalation scheme
  - Stopping criteria
  - Blinding
  - Placebo



THANK YOU

Any Questions?