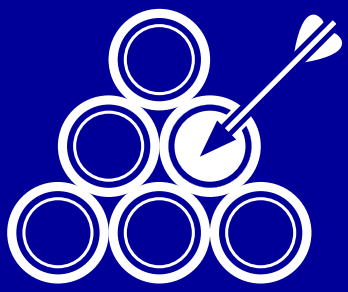
evotec

#RESEARCHNEVERSTOPS

INDiGO-*Select:* PROFILING AND SELECTING YOUR OPTIMAL CLINICAL DEVELOPMENT CANDIDATE

- Enhanced quality profile, speed of delivery, and probability of success of clinical candidates
- Early identification of developability gaps and liabilites in selection process, enabling thorough de-risking of your candidate with flexible advanced lead optimisation approaches
- Managed by skilled discovery scientists and complemented by experienced drug development experts in CMC and preclinical development all *under one roof*

Evotec believes in integrating discovery and development early in the process, to reduce risks and improve the probability of success in drug development. Our approach offers early evaluation of potential drug development issues during the lead optimisation phase, and prior to candidate selection. Ultimately, this improves the risk profile and knowledge of your candidate and ensures a smooth transition from preclinical to clinical development.



info@evotec.com | www.evotec.com

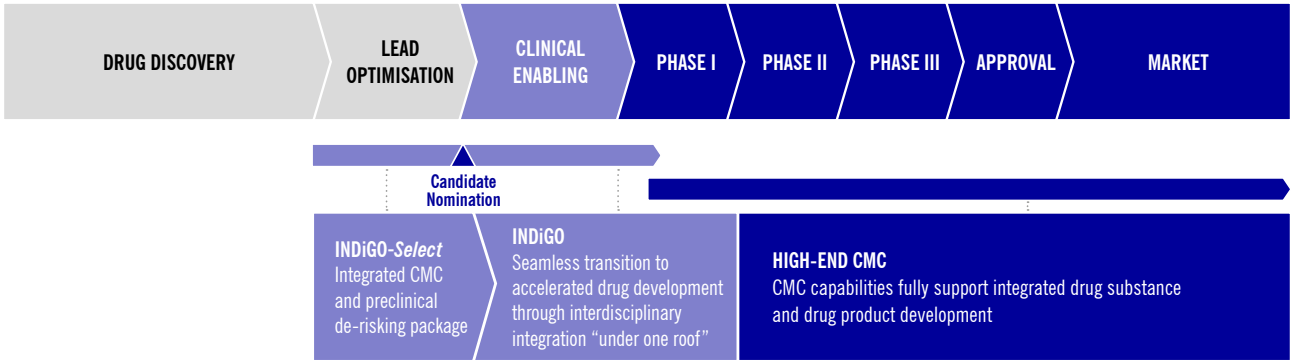
The road to the clinic is difficult enough without the inefficiencies of traditional drug development.

Evotec offers a two-tiered approach to the clinic:

- **INDiGO-*Select*:** For a single or short list of candidates, this integrated package will fully de-risk your molecule before investing millions and months in clinical-enabling studies. In addition, this package will enhance the quality, speed of delivery, and probability of success for your clinical candidate. Recommended in cases where drug discovery has been done outside of Evotec.
- **INDiGO:** Once your clinical candidate is selected, this fully-integrated clinical-enabling package focuses intensely on interdisciplinary coordination of all aspects of drug development, conducted and managed by a single Evotec team, and at a single Evotec site.

In bringing your candidate through IND filing "under one roof", we will eliminate the inherent inefficiency of the traditional multiple-vendor approach by consolidating development to a single, cross-functional point of contact and team with decades of drug development experience. All while increasing the probability and speed of success of your program.

Enhancing the probability of success for your lead molecule: lead candidate de-risking



INDiGO-*Select*

Thorough developability evaluation of "shortlist" of candidates or single compounds:

- Identify best compound for progression based on Target Product Profile requirements
- Identify gaps in knowledge base and develop a plan to resolve
- Address risk points in the program early in the process

End result: Higher probability of survival and shorter timeline to the clinic

WHY INDiGO-*Select?*

- Drug Discovery & Development is unpredictable and strategies change dynamically based on the properties of the compound as they are determined. Our platform is specifically designed to provide the necessary flexibility to adapt to these changes.
- Cross-functional integration under one roof enables Evotec to modify critical path assays and complex secondary characterisation based upon the specific characteristics of the compounds selected.
- The identification of vulnerabilities in a candidate, and the lessons learned on the chemical class throughout the INDiGO-*Select* program and prior to clinical-enabling studies is crucial to your confidence in your candidate. Not only does this approach allow you to select the optimal candidate, it provides the basis of understanding necessary to progress through clinical-enabling studies in the fastest possible time frame.

- Our two-tiered approach reduces your cost and timeline exposure in the event of a critical failure in meeting your developability metrics:
  - Tier One: Critical studies are conducted first, following a small-scale manufacturability assessment, ensuring efficient compound use
  - Tier Two: Following a second manufacturability assessment at a slightly larger scale, less critical tests or assays are conducted, typically requiring larger amounts of material than are conducted upon passage through Tier One
- Our unique cross-functional offerings allow for the incorporation of specific endpoints when necessary, tailored to the compound type, mechanism of action, clinical indication, and desired TPP
- Evotec has proficiency in multiple indications and can support Lead Optimisation not only via developability assessement but also via further qualification of primary pharmacology properties using transational modeling

Tier One: *In vitro* DMPK and safety

Compound synthesis on 2–5 g scale with initial assessment of route for scale-up

DMPK & PRELIMINARY MATERIAL SCIENCE

- Metabolic profile in hepatocytes (human and preclinical species)
- *In vitro* CYP450 inhibition (2B6 and 2C8), induction (mRNA levels using human hepatocytes) and identification
- *In vitro* transporter studies (i.e. substrate and inhibition) based on target and therapeutic area
- Rat single ascending dose study
- Pharmacokinetics in dog or NHP (IV/PO)
- Advanced prediction of human PK parameters and likely therapeutic dose
- Preliminary solid state, salts evaluation

SAFETY

- Off-target liability testing
- hERG (automated patch-clamp recording) – if not conducted earlier
- Nav1.5 and Cav1.2 assays
- Cardiomyocyte testing (if appropriate)
- Ames test on *Salmonella typhimurium* TA1535, TA1537, TA98 & TA100 and *E coli* strains, +/-S9
- Mitochondrial toxicity (e.g. Glu/Gal assay and SeaHorse assay)
- Liver toxicity (HepaRG 14 day assay)
- BSEP Inhibition (IC_{50} determination);
- GSH trapping assay (human & preclinical species)

Tier Two: CMC evaluation and *in vivo* safety

Preparation of ~10 g of selected candidate compound (with fit-for-purpose analytical support)

MATERIAL SCIENCE AND FORMULATION

- Physico-chemical characterisation of the compound (salt and polymorph screening) – if not done earlier
- Assessment of potential phototoxicity
- Formulation screening (or development) including bio-enhancing formulation strategies depending on API properties

***IN VIVO* SAFETY**

- Repeat dose tolerability assessment in rodents
  Testing at doses representing multiples of the predicted therapeutic exposure
- MTD in dog or NHP (preferred)
- CV anaesthetised guinea pig or other species (if required based on the type of CV risk identified, if any)

API: Identification of a scalable synthetic chemical route

evotec

#RESEARCHNEVERSTOPS

EVOTEC INDiGO-*Select*

Partnering with the experts

Benefits of evaluating development issues during discovery: integration enhances quality, speed of delivery and probability of success

- Addressing liabilities early solves problems at lower cost while there are more options and flexibility for modification
- Integrated processes create smooth progression, minimal handovers and easy communication throughout combined discovery and development teams
- High quality candidates, data packages and rapid progression maximise probability of success, value of the asset and minimise cost

Importance of a well-designed de-risking approach

- A relatively small investment at the candidate selection stage allows early identification of developability liabilities and challenges and consequently leads to rapid decision-making
- There are two main types of liabilities/challenges:
  - **Liabilities that can potentially result in compound termination:** as a result the financial impact may be not limited to the value of the development work up to termination but also the costs due to the delay in advancing alternative compounds (*e.g.* due to competition, etc.). This typically includes insufficient safety margins (*i.e.,* poor safety and/or efficacy)
  - **Liabilities that, if not managed earlier and properly, may not result in compound termination but still can delay the project** (up to months) and add significant extra costs due to additional work required, for example: chemical route not scalable, poorly soluble compounds, undefined salt/polymorph

Key attributes

- Flexible and dynamic structure allows real-time changes to strategy based on compound properties addressing liabilities early, saving time and money
- Modern & efficient tailored discovery programs with fit-for-purpose screening cascade
- Early integration of development allows learnings on the chemical class and identifies weak areas for optimisation of the ideal candidate molecule
- Managed by drug discovery and development experts with decades of industry experience

Find out how Evotec INDiGO-*Select can de-risk your candidate:*
Please contact us at info@evotec.com or visit www.evotec.com