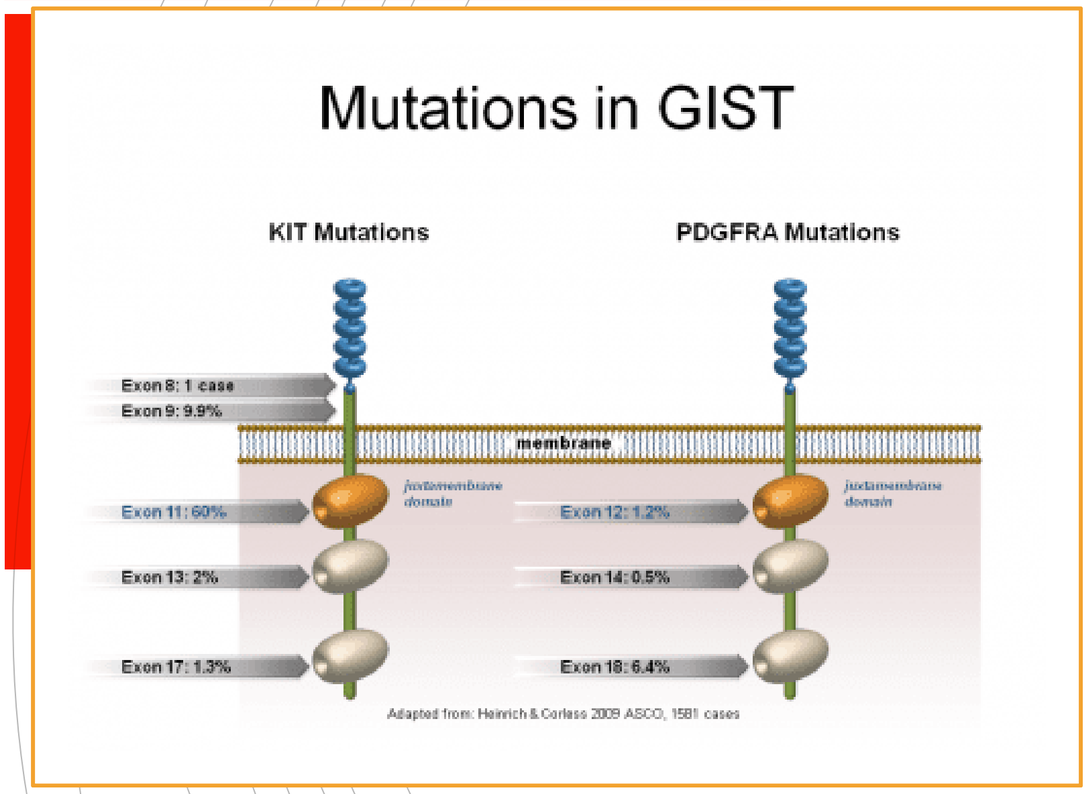
# Regulatory Plan for Ripertinib

# Table of contents

# Background Information on KIT and GIST




**KIT:** Receptor tyrosine kinase. This gene was initially identified as a homolog of the feline sarcoma viral oncogene v-kit and is often referred to as proto-oncogene c-Kit. Mutations in this gene are associated with gastrointestinal stromal tumors, mast cell disease, acute myelogenous leukemia, and piebaldism.

**GIST:** A gastrointestinal stromal tumor (GIST) is a type of cancer that begins in the digestive system. GIST s happens most often in the stomach and small intestine. A GIST is a growth of cells that's thought to form from a special type of nerve cells. These special nerve cells are in the walls of the digestive organs.

# Background information on Ripertinib


- Ripretinib is an orally administered switch-control kinase inhibitor engineered using our proprietary drug discovery platform and developed for the treatment of gastrointestinal stromal tumor, or GIST. Ripretinib is a KIT and PDGFRA switch-control kinase inhibitor that blocks initiating and resistance KIT mutations in exons 9, 11, 13, 14, 17, and 18 known to be present in GIST patients.

# Ripertinib development phase


- Ripertinib is currently in Phase 3 and the study completion was estimated to be in December 2024.

# Regulatory Pathway


Ripertinib is undergoing the regulatory approval process in approximately 125 centers globally. Key locations for its licensing include the United States, Argentina, Australia, Belgium, Canada, Chile, the UK, and Taiwan. The primary regulatory authorities involved in the drug development process are the FDA (United States), TGA (Australia), Health Canada, MHRA (UK), and TFDA (Taiwan).

# Competitors landscape


- **In the competitive landscape for ripertinib, several alternative drugs developed by other companies are in development:**

- **Imatinib (Gleevec) by Novartis**:
  Currently in Phase 2 of clinical trials.

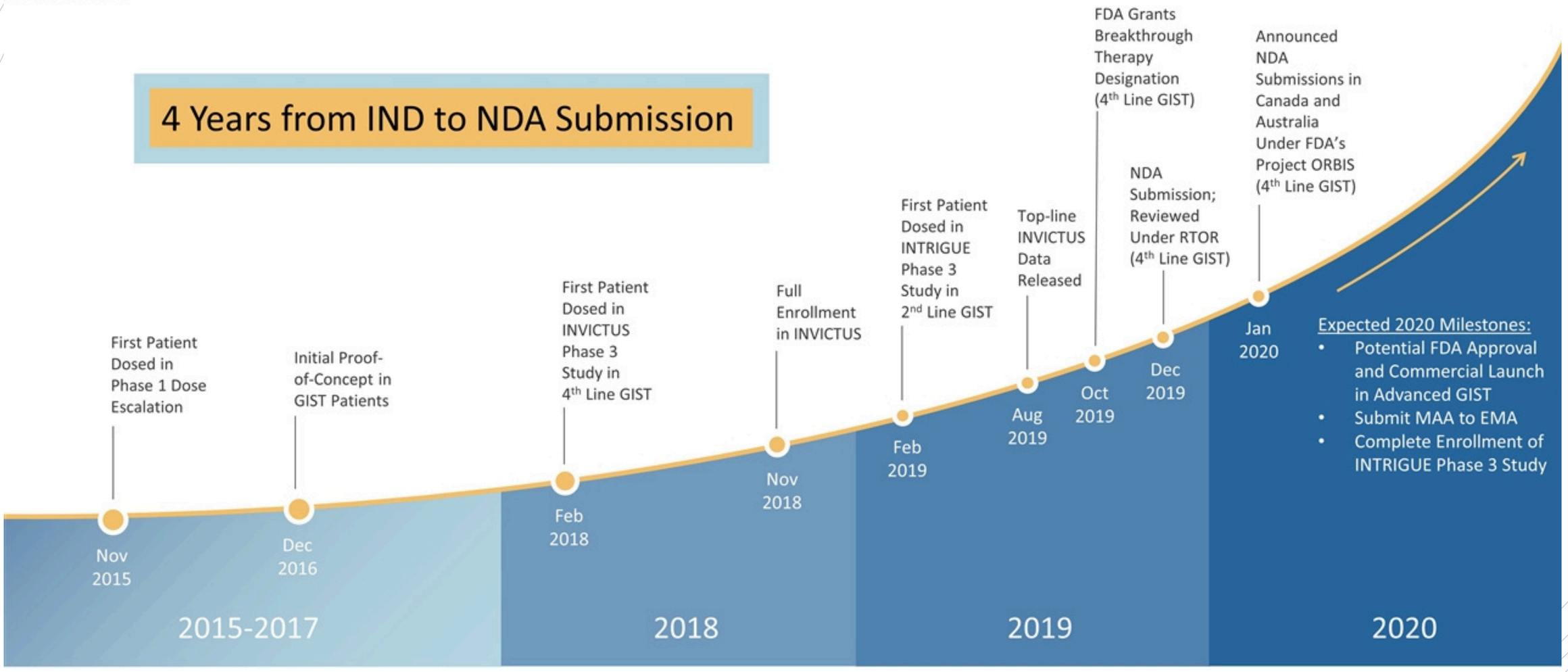
- **Regorafenib (Stivarga) by Bayer**:
  Currently in Phase 2 of clinical trials.
  Features a single group assignment design, unlike imatinib and ripertinib, which utilize parallel assignment.

**Avapritinib by CStone Pharmaceuticals**:
Developed by a Chinese company

| Phase | Study Description | Key Findings |
|---|---|---|
| **Phase 1** | First-in-human study in GIST and advanced solid tumors to determine dose and evaluate safety and efficacy (142 patients). | - **ORR:** 19.4% (2nd-line), 14.3% (3rd-line), 7.2% (4th-line+)<br>- **PFS:** 10.7m (2nd-line), 8.3m (3rd-line), 5.5m (4th-line+)<br>- Supported further development in 2nd-line+ GIST. |
| **Phase 2** | No dedicated Phase 2 study. | - Phase 1 results supported moving to Phase 3 INVICTUS trial. |
| **Phase 3** | INVICTUS trial in advanced GIST (129 patients) comparing ripretinib to placebo. | - **PFS:** 6.3m (ripretinib) vs 1.0m (placebo)<br>- **ORR:** 9.4% (ripretinib) vs 0% (placebo)<br>- **OS:** 15.1m (ripretinib) vs 6.6m (placebo)<br>- Supported FDA approval. |
| **Registration** | FDA approval based on INVICTUS trial results. | - **FDA Approval:** May 15, 2020, for advanced GIST after ≥3 kinase inhibitors, including imatinib. |

# Regulatory plan

# **Ripretinib:** Rapid Clinical Development



# RISK REGISTER

| Risk ID | Risk Description | Impact Level | Probability | Mitigation Strategy | Contingency Plan |
|---|---|---|---|---|---|
| 1 | Delay in trial enrollment | High | Medium | Increase site engagement and patient outreach | Extend enrollment period, add more sites |
| 2 | Adverse safety findings | High | Low | Close monitoring, safety reviews, immediate reporting | Adjust dose, halt trial if necessary |
| 3 | Insufficient efficacy results | High | Medium | Interim analysis, adaptive trial design | Reevaluate trial endpoints, modify study design |
| 4 | Regulatory non-compliance | High | Low | Regular audits, compliance training | Address findings immediately, enhance compliance protocols |
| 5 | Manufacturing issues | Medium | Low | Secure multiple suppliers, rigorous quality control | Shift production to alternate supplier, maintain inventory stock |
| 6 | Intellectual property disputes | High | Low | Thorough patent research, legal consultation | Legal defense, explore licensing agreements |
| 7 | Changes in regulatory requirements | Medium | Medium | Continuous regulatory surveillance, proactive communication | Adjust development plan, engage with regulatory authorities |
| 8 | High dropout rates | Medium | Medium | Enhance patient support and follow-up | Increase patient engagement efforts, offer additional support |
| 9 | Data management issues | Medium | Low | Robust data management plan, regular data audits | Implement data recovery procedures, enhance data security |
| 10 | Funding shortfalls | High | Low | Secure diverse funding sources, budget contingency | Seek additional funding, adjust project scope |

# THANK YOU