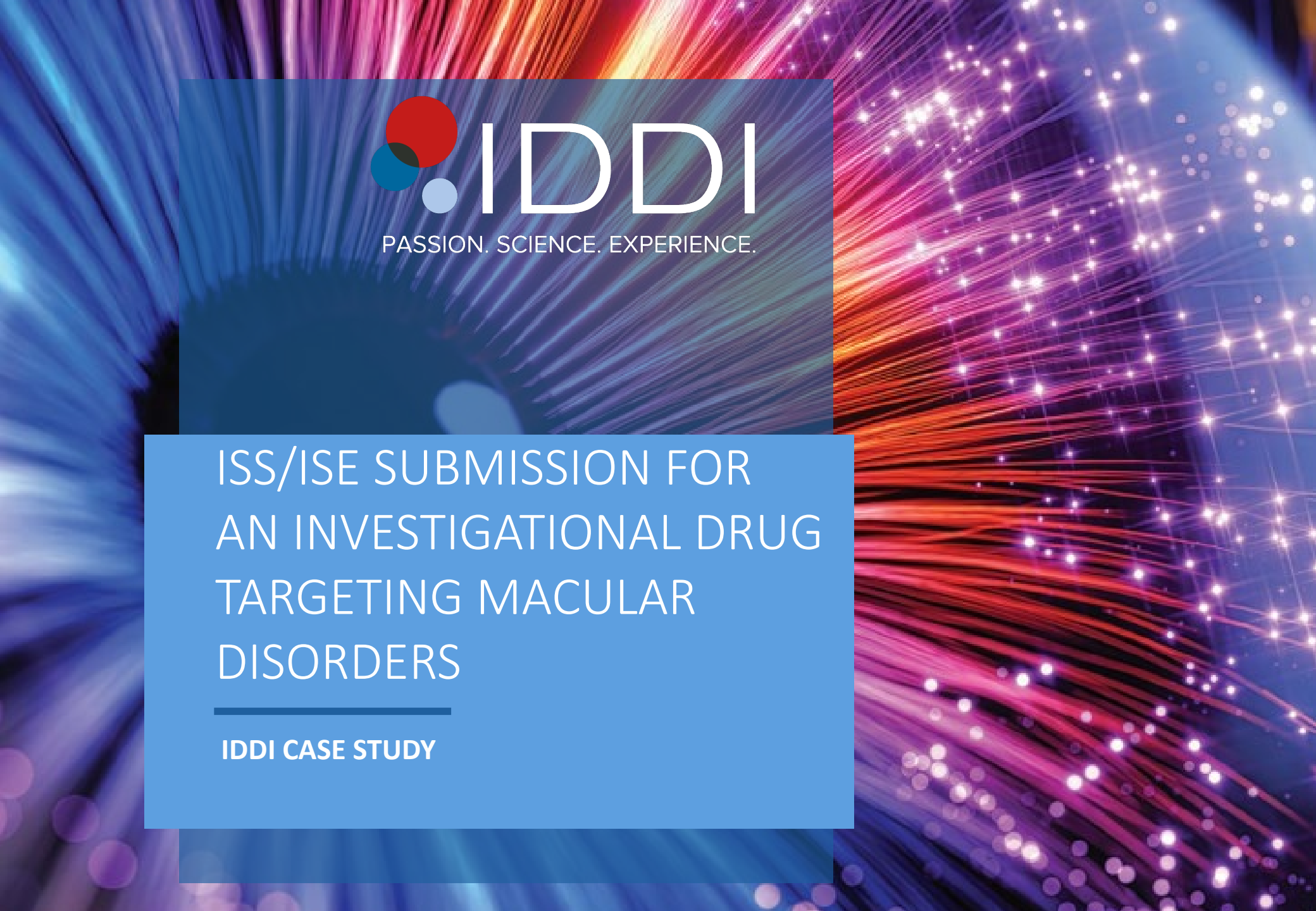


ISS/ISE SUBMISSION FOR AN INVESTIGATIONAL DRUG TARGETING MACULAR DISORDERS

IDDI CASE STUDY

STUDY

INVESTIGATIONAL DRUG TARGETING MACULAR DISORDERS

- Geographic Atrophy (GA)
- Neovascular Age-Related Macular Degeneration (nAMD)
- Idiopathic Polypoidal Choroidal Vasculopathy (IPCV)
- Autosomal Recessive Stargardt Disease (STGD1)

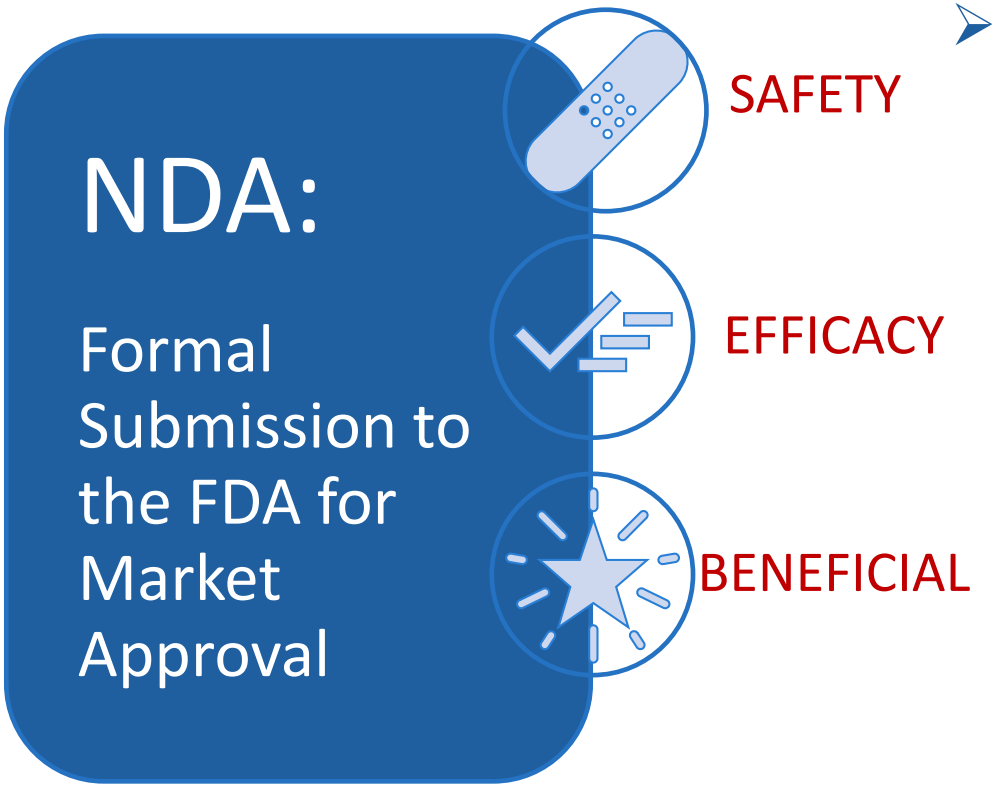
- **Administration**: Intravitreal injection
- **Clinical Trials**: Investigational ophthalmic drug was studied across multiple trials.

STUDY OBJECTIVES

The primary goal was to seek FDA approval through a New Drug Application (NDA).

- The application process included **submitting Integrated Summary of Safety (ISS) and Integrated Summary of Effectiveness (ISE) reports,** which combine data from multiple trials to assess the drug's overall safety and efficacy.

NDA DEFINITION



- A New Drug Application (NDA) is a **formal submission to the FDA, requesting approval to market a drug**.
  - It must contain sufficient data to demonstrate that the drug is **safe, effective, and beneficial**, with appropriate labelling and robust manufacturing controls **to ensure drug quality**.

ISS/ISE DEFINITION

- Integrated Summary of Safety and Integrated Summary of Effectiveness are **Regulatory submission documents** which are required by the FDA while filing a New Drug Application (NDA).
- The data from **all clinical trials** performed on the study drug are **pooled** together and analyzed as a whole, producing combined statistical results.

ISS	ISE
Identifies **risks**	Evidence for **dosage and administration**
Characterizes the **overall safety profile**	**Effectiveness** by **subgroup**
Evaluates **rare/unexpected trends** or **safety signals**	Substantial **evidence of effectiveness** for each claim

STUDY OBJECTIVES

The trials aimed to establish the drug's safety and efficacy, focusing on a 2 mg dosage to treat Geographic Atrophy (GA) patients.

SAFETY

- 2 mg dosage was demonstrated to have a safety profile comparable to or better than higher doses.

EFFICACY

- The trials sought to prove that the 2 mg dose was effective in treating GA, with results showing that it performed better than the 1 mg dose and was still clinically meaningful compared to the 4 mg dose.

ISS /ISE POOLING STRATEGIES

The pooling strategies for the ISS and ISE submissions grouped data by cohorts, based on the trial design and the condition being treated:

ISS Pooling Strategy:

- **COHORT 1**
  Clinical trials in GA examining the safety profiles of different drug doses
- **COHORT 2**
  Trials in AMD assessed shorter-term safety outcomes
- **STUDY FOR IPCV**
  Supportive data for safety outcomes
- **STUDY FOR STGD1**
  Supportive data for safety outcomes

ISE Pooling Strategy:

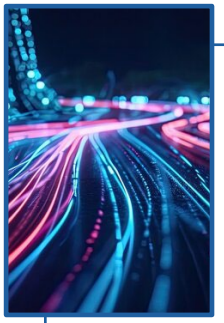
Focused on GA trials, analyzing the efficacy by examining the rate of GA progression and changes in visual acuity.

CONSTRAINTS AND CHALLENGES

Throughout the submission process, the following challenges were noted:

Data Standardization

- Some trials required re-mapping to fit current standards.



Inconsistent Data

- Variations in coding dictionary versions , visit windowing, and data collection (e.g., ECG results) caused discrepancies.

Short Timelines

- The need to address these challenges under tight timelines was a significant constraint.

SOLUTIONS

To address these constraints, in parallel to other activities, the IDDI team took the following actions:

Re-mapped older trials to current data standards.

Re-coded inconsistent data to align with the latest coding dictionaries.

Implemented solutions to handle data inconsistencies, including ad-hoc displays for irregular findings.

Assigned IDDI's dedicated resources for ISS/ISE

Held weekly meetings to manage the fast-paced work, ensuring all activities were on track.

CONCLUSIONS

This case study highlights the complex process of compiling an NDA submission, particularly when pooling data from multiple trials with varying standards.

- Despite the constraints, the proactive steps taken by **IDDI's team ensured that the ISS/ISE submissions provided robust evidence to support the FDA's evaluation of the drug.**

- The ongoing trials and **pooling strategies have built a comprehensive profile of the drug safety and efficacy in treating macular disorders.**

✓ FDA granted Approval for Geographic Atrophy on August 5, 2023

✓ EMEA accepted the drug's Market Authorization Application for Geographic Atrophy on August 18, 2023

CONTACT US

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ABOUT IDDI

International Drug Development Institute (IDDI) is an expert organization in **Regulatory Statistics and Clinical Data Science**, committed to assisting pharmaceutical, biotech, medical devices, and Cooperative Groups in several disease areas, with a special focus on oncology, ophthalmology, CNS and Rare diseases.
Founded in 1991, IDDI has offices in Belgium, and Raleigh (NC).

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