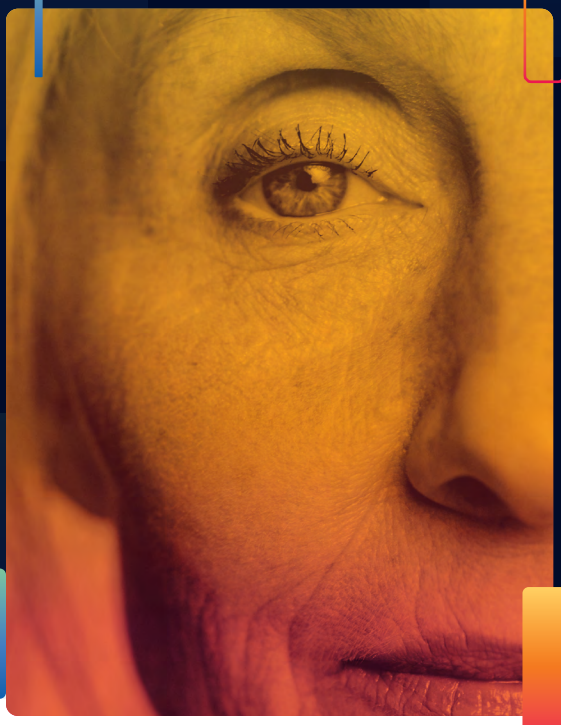


CASE STUDY

ISS/ISE Submission For An Investigational Drug Targeting Macular Disorders

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.

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.

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

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

The trials aimed to establish the drug's safety and efficacy, focusing on a 2-mg dosage to treat **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

The submission process faced three main challenges:

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

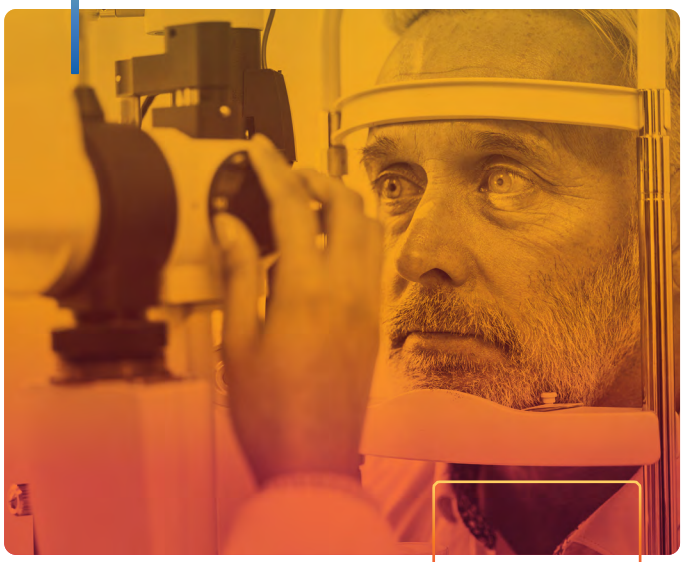
To address these constraints, in parallel to other activities, the IDDI team:

- 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 GA on August 5, 2023**
- **EMEA accepted the drug's Market Authorization Application for GA on August 18, 2023**



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