Leadership and Innovation
Paper LI–07

Scaling within a fast-moving Biotech company
Key learnings for leaders and innovators

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ABSTRACT

“Build the plane while flying it” is probably a good quote for the journey ahead of us. Argenx is a fast-moving and growing Biotech company. This means we need to rapidly scale for future success while delivering on the ongoing clinical trials and submission milestones. In this paper, we focus on the journey so far as well as the future ahead of us.

This includes an analysis of the argenx processes, talents, system landscape, and adoption of industry standards within Data Management. Next, mapping these to the future needs including integrations and automations, identifying potential gaps, and most importantly creating a business plan with realistic timelines for management approval. Finally, moving into the implementation phase, following up on the plan as agreed with leadership.

COMPANY OVERVIEW

REACHING PATIENTS THROUGH IMMUNOLOGY INNOVATION

Argenx is a global immunology company, committed to improving the lives of people suffering from severe autoimmune diseases. Established in 2008, starting out with partnering programs and a focus on strong science, it wasn't until 2015 when the first healthy volunteer trial was designed, followed by a first phase II trial one year later.

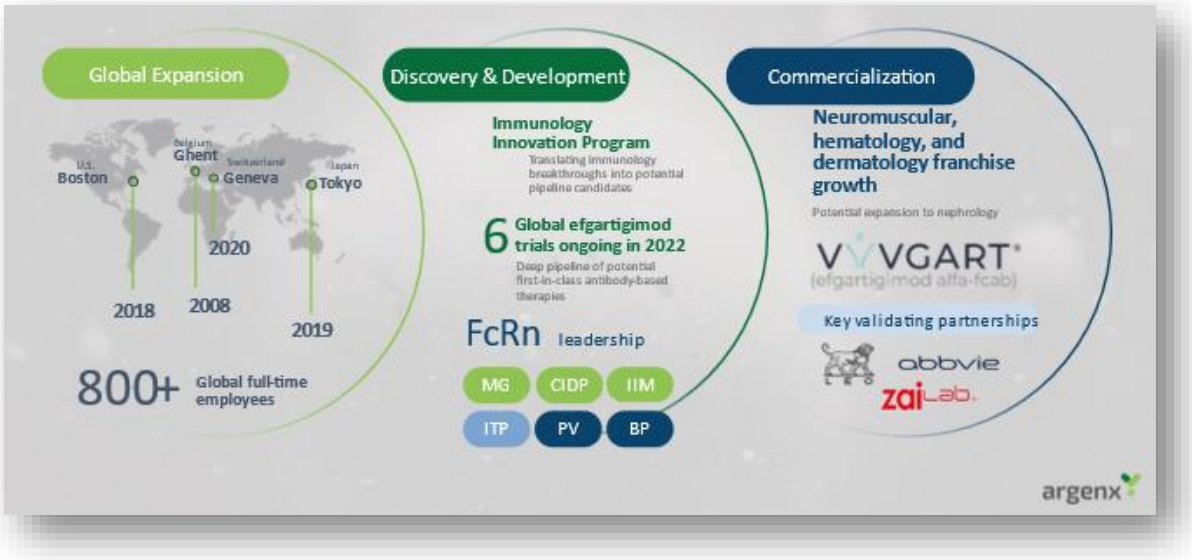

Figure 1 - Immunology Innovation and collaboration

The data management group was established in 2018, meaning that until then we relied solely on the infrastructure provided by our partners. 2019 called for a change in strategy, around the time when argenx was planning its first submission to regulatory authorities in the following year.

This meant that within a timespan of less than 2 years, we needed to update our quality management processes, build an infrastructure to maintain our data and be inspection ready while running the daily business and adhering to already challenging timelines.

Fast forward 2 years later, and by the end of 2021, argenx had its first product approved and a very ambitious pipeline ahead. Our barebones infrastructure was in place by this time, but among others, the COVID-19 pandemic has taught us that the market for talent is very competitive, good resources are becoming scarce, hence we saw the need to invest further in a fit-for purpose environment, including the right people, the right partners, optimized processes, and the appropriate platforms to support all this.

Figure 2 - argenx 2025 plan

THE EVOLUTION OF CLINICAL DATA MANAGEMENT

DRIVING FORCES

Since the release of the first reflection paper in June 2019 by the Society for Clinical Data Management (SCDM), the core drivers of the Clinical Data Management (CDM) evolution toward Clinical Data Science (CDS) remained consistent and centered around four main themes.

- **The complexification of clinical trials designs** (e.g., Adaptive, Master Protocols, Synthetic Control Arms) where studies regularly include different patient populations and endpoints with evolving and flexible study characteristics.
- The **decentralization of clinical trials (DCT)** accelerated by the COVID-19 pandemic. This is leading to a wider adoption of patient centric solutions such as telemedicine, home nursing and electronic consenting. A DCT framework allows patients to decide what suits them the best (i.e., being Patient-Driven). However, the volume of direct data capture (i.e., eSource) clearly challenges the centricity of traditional EDC technology and processes relying on site source's transcription, SDV and queries.

Figure 3 - Driving Forces behind evolution to CDS

- The **adoption of risk-based CDM approaches** fostering Quality by Design (QbD) and the focus on what matters the most (i.e., Critical to Quality (CtQ) Factors, critical data and processes) according to the latest ICH E6 (R2) and ICH E8 (R1) guidelines.
- The **automation of CDM activities leveraging maturing intelligent technologies** acting as virtual assistants to the Clinical Data Scientist. Some technologies consist in automating repetitive and reproduceable activities using Robotic or Intelligent Process Automations (RPA & IPA) such as data transformation and reconciliation.

Other advance capabilities such as Machine Learning (ML) or Natural Language Processing and Generation (NLP & NLG) can automate more complex activities such as query detection and query writing as well as predicting data issues.

Additionally, as we evolve, it is critical to remind ourselves to go beyond data integrity (i.e., achieving data quality). While ensuring data integrity is essential, reaching data quality to ensure the reliability of the trial results is at the core of our evolution and is fundamentally changing the way we manage data by focusing more on its meaning and its value.

For more information on the evolution into a **CDS organization** check out the recent SCDM Position Paper.

WHERE IS ARGENX ON THIS JOURNEY…

Clinical Research 2.0

At argenx, we've created an antibody innovation ecosystem where pioneering scientists and antibody engineers work side-by-side to accelerate the discovery of novel targets, disease pathways and differentiated therapeutic antibodies.

Efgartigimod is designed as a first-in-class investigational antibody fragment to target the neonatal Fc receptor (FcRn). Efgartigimod is being evaluated for the **treatment of patients with severe autoimmune diseases** with confirmed presence of pathogenic immunoglobulin G, IgG autoantibodies, where a severe unmet medical need exists.

Due to the nature of these rare autoimmune diseases we are at the **forefront of complex trial designs.** Each of our trials is **adaptive** in nature.

Decentralized Clinical Trials

We are still at the early exploratory phase when it comes to **Digital Endpoints & Biomarkers** making use of sensors/wearables.

Other decentralized technologies / processes such as **Telemedicine** (remote video/audio calls), usage of **electronic Clinical Outcome Assessments** (eCOA) and **study assessments at home** (assisted by 3rd party staff), are standard practice for most of our complex trials - since the inception of the company.

Another great example is MyRealWorld™ MG which is a **global observational (real world) study** to assess the impact of Myasthenia Gravis on patients' lives. Working with patient organisations from 10 countries (US, Japan, Germany, UK, France, Italy, Spain, Canada, Belgium and Denmark), argenx sponsors this innovative study. The study is open to anyone diagnosed with Myasthenia Gravis, 18 years or older. It includes regular questionnaires and surveys about the diagnosis, symptoms, treatments, activities and quality of life. It also includes a medical profile where treatment data can be recorded.

Risk Based Approaches

We are a small biotech company with a very rich pipeline. Keeping the entrepreneurial DNA of this company while scaling for success is crucial. We can only achieve this by **adopting in everything we do (end-2-end) a Risk Based Approach.**

Risk-based quality management (RBQM) is a strategy for managing quality throughout a clinical trial. The data-driven elements of this type of strategy have evolved over the past few years, as an extension to the original principles of risk-based monitoring (RBM). At argenx **we design simple processes, explore and implement smart technologies, and focus on change management.**

Quality by Design sessions (days) are organized to share experiences across the organization. Some examples of topics are experiences of first launches in Japan; the implementation of the EU Clinical Trial Regulation (CTR) - The largest change in Clinical Trial Regulation in Europe since the implementation of the Clinical Trial Directive 20 years ago; quality in global patient safety and the EU launch journey.

As we are running more clinical trials of efgartigimod for a range of different autoimmune diseases, there is also a shift in focus from First Patient In (FPI) to Last Patient Visit (LPV) for these trials.

Protocol Design has been therefore defined as a company top priority in 2023 avoiding lots of protocol amendments; especially due to the new CTR in EU i.e. only one substantial amendment allowed at the same time (45–86 calendar days).

Intelligent Technologies

When it comes to intelligent technologies leveraging advanced analytics including Artificial Intelligence (AI) / Machine Learning (ML) we have not yet started this exciting journey ahead of us.

Reasoning is that we have been focusing the last 3 years on **establishing a strong foundation** for future growth - see next chapter... or as Vas Narasimhan (CEO – Novartis) already stated in 2019, “yes AI – But First, Data”.

ESTABLISHING A STRONG FOUNDATION

2019-2021 TRACK RECORD

As a fast growing company with upcoming submissions to multiple regulatory authorities we decided to focus first on establishing a strong foundation for **efficiency; scalability and de-risking staff dependency**.

One of the first priorities was the need to have a **Structured Data Repository** and **Statistical Computing Environment** in place for Clinical Development (and beyond) in alignment with the following key requirements:

- ✓ Storage and maintenance of clinical and analysis data / documents
- ✓ Collaborative Work Environment: Internal and External
- ✓ Support development and execution (production) of programs: SAS, R, ...
- ✓ Reproducibility & Traceability of analysis
- ✓ Configurable; managed Centrally (Cloud); Secure Storage; Easy Retrieval of data & documents
- ✓ Must be Open to interact easily with other applications: APIs and other integration capabilities
- ✓ Technical Req's (detailed list – internal only)
- ✓ Regulatory Req's (detailed list – internal only)

We also wanted to have this in place (in production for usage by business groups) **within 3-6 months**. These timelines include requirements gathering; budget approval; vendor selection and implementation. All within a GxP Qualified environment in the cloud and managed by a specialized vendor in our industry with a significant track record. Important to note is that **argenx strongly believes in partnerships and outsourcing model** (Pharma/Biotech, CROs, Tech Companies, Academia,...); only added (core) value activities should be done internally. It is not the intention to expand the company with 3x as much employees, we rather want **to build and leverage eco-systems to grow as a company.** Taking into account all these criteria, SAS Institute & OCS Consulting were selected as strategic partners, leveraging the SAS Life Science Analytics Framework (SAS LSAF) as the underlying technology framework.

Another key focus area was the **creation of a standards governance team and process** within clinical development.

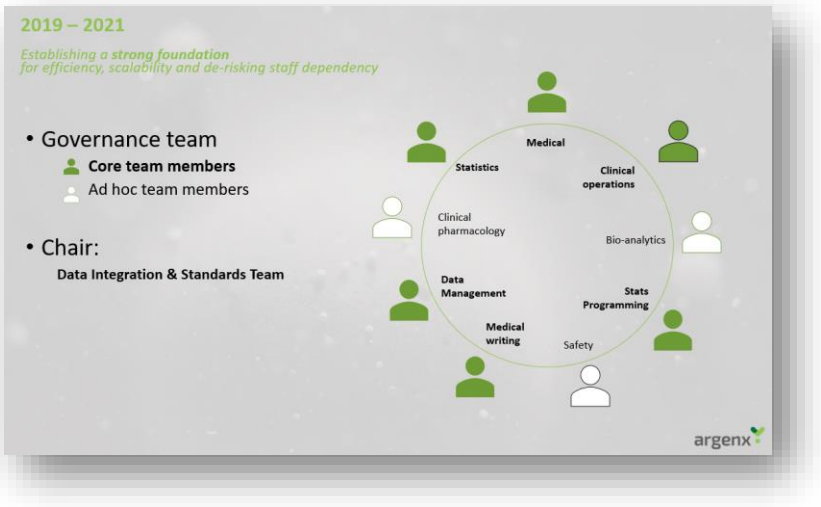

Figure 4 – argenx Governance Team

The Data Integration & Standards Team (within Data Management) acts as the chair for these monthly governance meetings. This team prepares the monthly standard topic(s), often linked to the standard packages (batches) under development.

Once there is consensus within the Data Integration & Standards Team, a review / input cycle is foreseen by the Data Management Leads (DML's). Individuals from the governance team (such as Bio-Stats, Medics, Clin Ops) might be consulted along the way. Only afterwards a final proposal is shared with the full Governance team - before the monthly meeting - to allow for review time. Final discussions take place during the monthly meeting to be able to close the topic and move on to the next on the priority list.

Data Standards packages do include at minimum Unique CRF Forms; SDTM annotations; CRF Completion Guidelines; SDTM Metadata (Define); Data Validation Specs; Data Transfer Agreements (DTAs) and Naming Conventions.

Once the standards governance team and process was in place we started working on the next foundational priority. The **need for a Clinical Metadata Repository to move away from** spreadsheet-based standards and drive automation and scalability.

The following key requirements were defined:

- ✓ Develop, maintain, and govern the argenx clinical data standards, both front end (CRF visualizations, Completion Guidelines, Checks) and back end (SDTM/define)
- ✓ Optional extension: incorporate analysis standards (ADaM/define) and non-clinical data standards (SEND/define)
- ✓ Configurable; managed Centrally (Cloud); Secure Storage
- ✓ Must be Open to interact easily with other applications (i.e. Metadata driven automations)
- ✓ Technical Req's (detailed list – internal only)

Taking into account all these criteria, Formedix was selected as strategic partner, leveraging Ryze as the underlying technology framework.

For a deeper dive on this specific topic please read the PHUSE EU Connect 2022 paper (SI05) - Maturing standardization. The switch from spreadsheet-based standards to an MDR by Jasmine Kestemont and Louella Schoemacher.

AS-IS VERSUS TO-BE (PROCESS EXCELLENCE)

SHORT TERM – 2022/2023

So far we have explained the status “as-is”. But what’s next? What’s our short term ambition. One common ask from multiple stakeholders is **the need for more near-real time data flows**.

Today we receive monthly SDTM transfers from our DM-CROs. This means we only have monthly refreshes of our data for DM Trial Oversight; for creation of generic ADaM and Patient Profiles (by our Quantitative Sciences colleagues); for medical review and many more. Establishing a near-real time data flow is therefore “the” next priority.

We started executing on the plan to **pull in weekly (or ad-hoc daily) EDC data** from our RAVE URLs (managed by our DM-CROs & Medidata) **as well as Ancillary Data** (e.g. Central Lab/ECG) into our SAS LSAF environment. Having these data available near-real time will allow us to **generate generic SDTM data** for DM-CRO trial oversight and downstream processing by QS and other stakeholders. We foresee to automate these data flows through APIs and other integration capabilities as well as implementing workflows in LSAF.

In parallel we started to explore **industry data ‘mapping’ tools** that we can leverage to **accelerate** the creation of SAS code for the generic SDTM data. One critical requirement is that this accelerator need to be open (not closed black box) and integrate (co-exist) with our Formedix Ryze and SAS LSAF environments.

On the standards level we keep building our global libraries in close collaboration with the Standards Governance team and implementing these in the Ryze MDR system. At the moment we are focusing on **global standards** that are applicable for all argenx trials. During the course of 2023 we are planning to scale and work also on **Indication level standards**.

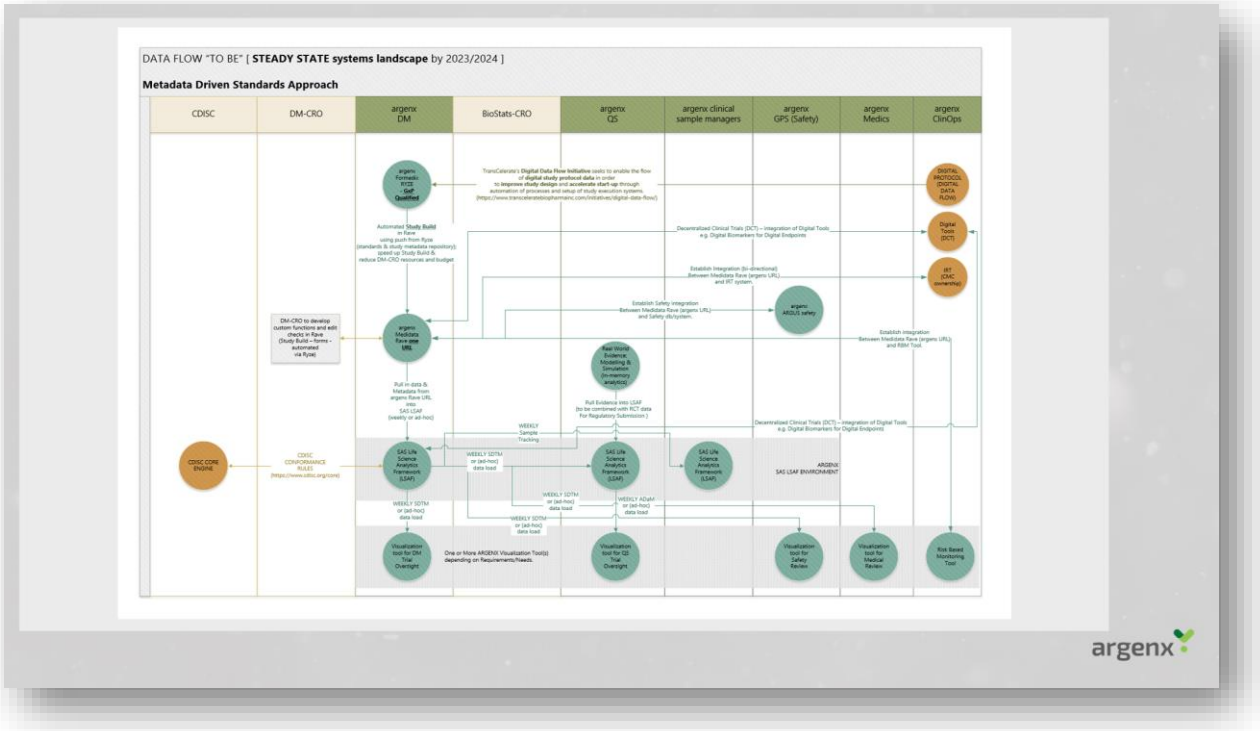

Figure 5 - STEADY STATE systems landscape (2023/2024)

Moving to a truly **Metadata driven trial setup** we started in Q4 **leveraging these available global data standards in Ryze** (Forms & SDTM Metadata) to build our first real trial level specs / metadata. In addition we loaded the Rave Architect Loader Spreadsheet (ALS) and SDTM Define from an existing trial to be able to **leverage Indication specific forms & SDTM metadata.**

A first deliverable was a unique CRF for Ethical Committee approval and soon we will also share with the DM-CRO our first SDTM Metadata /define specs. This will enable the DM-CRO to build the eCRF in Rave and creates efficiencies end-2-end.

During study conduct we will be able to **compare 'out of the box' the metadata and data** we will receive monthly from the DM-CRO with our own metadata specs. In addition we will also be able to compare our own generic SDTM data with this metadata and the DM-CRO datasets.

Long term (2024), it is our goal to drive from the metadata in Ryze an automated build in Rave.

We are also working intensively towards **standard packages (QC Jobs/Programs)** in SAS LSAF to support our Data Managers with Trial Oversight. As a fast growing organization we need to increase our efforts on best practices and standardization across the globe.

Finally, we have **identified other system needs** such as Visualization Tools for Trial Oversight / Medical Review and RBM tool as presented on the Steady State System Landscape.

CONCLUSION (KEY LEARNINGS)

CRITICAL SUCCESS FACTORS

Looking back and looking forward, we identified 3 key themes that drove our success:

1. **Entrepreneurial Spirit**

   From defining the initial requirements, going through budget approval, vendor selection and implementation from start to finish the projects took between 3 – 6 months. Not everything was carved out in stone and we anticipated that we would learn along the way. This will not work for everyone or every project, but it suited us well during our journey.

2. **Empowerment and excellence**

   The ability to engage cross-functional teams with a mandate to decide on behalf of their function and with the same focus to deliver was instrumental in keeping the project on track. When decisions needed to be made, they were fact and data driven, transparency ensured that emotions and preferences were not the driving forces.

3. **Co-creation**

   We are a company that thrives on including the best and fit for purpose. If that means collaborating with another company that has already developed something, then that is the better choice. "not invented here" or "we've always done it that way" were excluded. On the other hand, we are a young company, hiring people with lots of experience, but with a clean slate to start from, which gave us the opportunity to do Quality by Design.

Looking ahead, we have also identified some key learnings, things we do not want to lose and things we would do differently in a next trial.

1. We are proud of our argenx “DNA”, as the company grows, **we want to keep the entrepreneurial spirit,** hence while selecting for diversity we will continue to focus on talent and creativity.

2. We need to **increase our level of standardization** … from protocol design to submission .. and beyond. This will allow further integration and automation.

3. We need to **continue to innovate** to ensure we can manage the pipeline ahead. This means that every once in a while, we will need to take a step back to reflect, while maintaining a high pace to deliver on the portfolio.

REFERENCES

[1]: argenx corporate presentations

Events & Presentations | Argenx

[2]: Society for Clinical Data Management – Position Paper Evolution into Clinical Data Science

https://scdm.org/wp-content/uploads/2022/09/SCDM-Position-Paper-Evolution-into-Clinical-to-Data-Science-V9.0.pdf

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