Accelerating Clinical Trials:
Use of Historical Subject Level Data
for Controls
The TransCelerate Placebo/Standard of Care Database

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Astellas Pharma
EFSPI statistics leaders meeting

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AGENDA

- *High-level overview of TransCelerate*

- *PSoC History, Milestones and Activities*

- *Current data available within the database*

- *Using historical data to substitute control arm*

What is TransCelerate?

2012
TransCelerate Founded

10 MEMBER COMPANIES

5 INITIAL INITIATIVES

2016
BioCelerate Founded

BioCelerate
focus on preclinical research

Today

19 MEMBER COMPANIES
Novartis most recent member

25+ INITIATIVES
including 4 pharmacovigilance initiatives

BREADTH & DEPTH
Over 30 solutions being delivered across 25+ initiatives, across 3 strategic priorities

CULTURE OF COLLABORATION
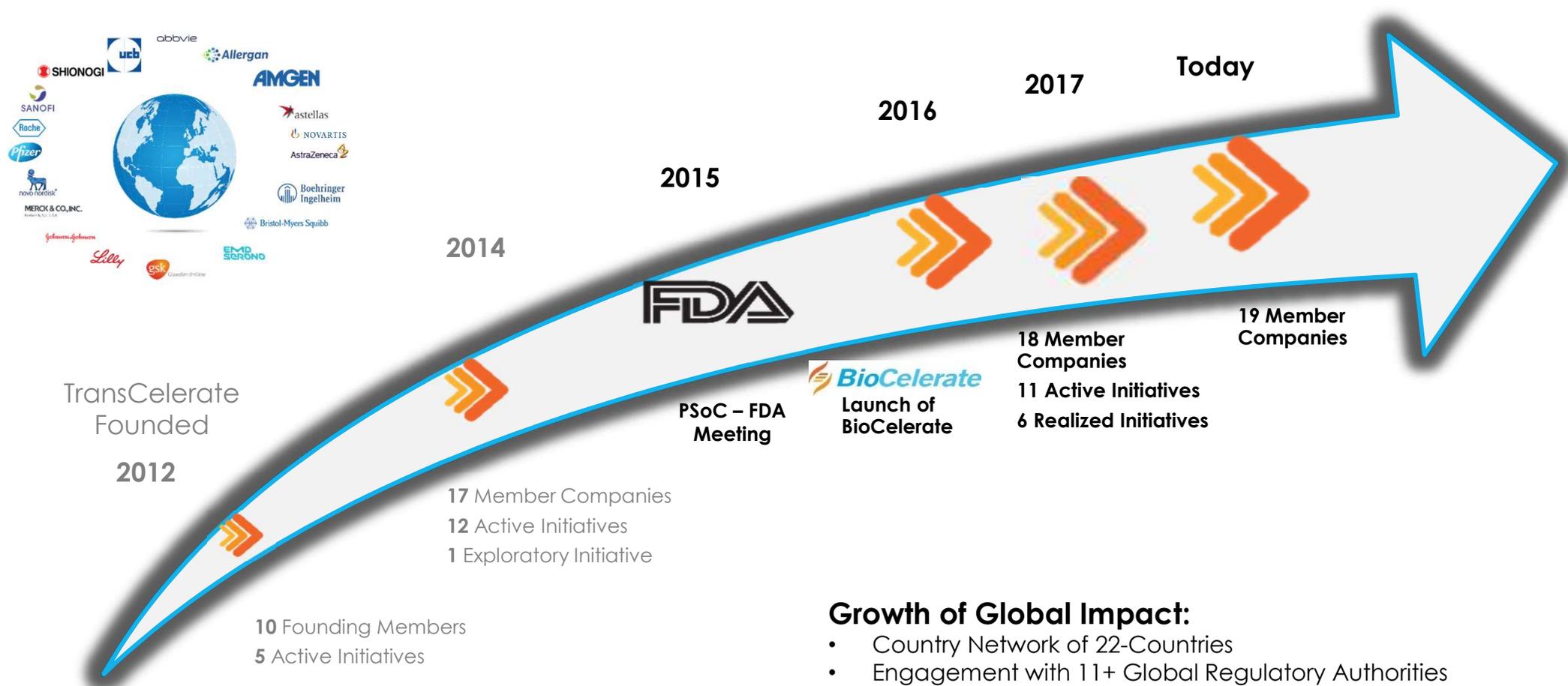With an effective and proven governance structure have increased the ease and desire to collaborate

ENABLING PLATFORM TRIALS
12+ initiatives deliver solutions that enable future platform trials

DataCelerate
platform to enable data sharing

TransCelerate has seen Significant Growth

TransCelerate Founded

2012

10 Founding Members
5 Active Initiatives

2014

17 Member Companies
12 Active Initiatives
1 Exploratory Initiative

2015

PSoC – FDA Meeting

Launch of BioCelerate

2016

18 Member Companies
11 Active Initiatives
6 Realized Initiatives

2017

Today

19 Member Companies

Growth of Global Impact:
- Country Network of 22-Countries
- Engagement with 11+ Global Regulatory Authorities

Placebo/Standard of Care Data Sharing

Unmet Need: Lack of ability to reuse data, leverage historical data, and utilize readily available context information

Objective: To establish a database to share de-identified Placebo and Standard of Care data

Benefits: Improved clinical trial design, faster clinical trial execution, ethical clinical equipoise, and a better understanding of disease

PSoC

PSoC History, Milestones and Activities

Whitepaper: guidance on the potential applications PSoC database and use case details

Manuscript: Minimizing Patient Burden through the Use of Historical Subject-Level Data in Innovative Confirmatory Clinical Trials

PSoC Multi-Stakeholder Workshop

	2014	1&2Q15	3&4Q15	1&2Q16	3&4Q16	1&2Q17	3&4Q17	1&2Q18	3&4Q18
Timeline									
Key Milestones	Establish workstream & defined use cases	Designed & Built the Data Sharing Database	10-MCs agree to share data; Database live	10-studies shared; 1st control arm data set leveraged	44 studies converted & 50,000 patients in database	85 studies & 75,000 patients in database	Manuscript Submission	16th MC joins PSoC	Continued Engagement with HAs, Academia

HA Meeting: FDA CPATH

HA Meeting: EMA engaged PSoC. FDA

Harvard: Pending Collaboration

The PSoC Data Sharing initiative seeks to operationalize key use cases that drive efficiencies

	Use Case	Value Drivers								
		Reduced Cycle Times	Decreased Development Costs	Avoid Post-Marketing Costs	Reduction of Patient Numbers	Reduction of Overpowering Studies	Phase 3 Trial Success	Reduced Protocol Amendments	Phase 2 Cost Reduction	Increased Safety/ Efficacy Signaling
1	Enhanced Safety Signal Interpretation	✓	✓	✓						
2a	Control Arm Substitution (Early Phase Trials)	✓	✓		✓					
2b	Control Arm Substitution (Late Phase Trials)	✓	✓		✓					
3	Precision Powering					✓			✓	
4	Inclusion/exclusion Criteria Optimization		✓			✓				
5	Disease Modeling Capabilities						✓	✓	✓	
6	Improved Understanding of Geographic Differences	✓	✓							
7	Biomarker Development	✓	✓	✓						✓

A key use case is control arm substitution or supplementation

	Use Case	Value Drivers								
		Reduced Cycle Times	Decreased Development Costs	Avoid Post-Marketing Costs	Reduction of Patient Numbers	Reduction of Overpowering Studies	Phase 3 Trial Success	Reduced Protocol Amendments	Phase 2 Cost Reduction	Increased Safety/ Efficacy Signaling
1	Enhanced Safety Signal Interpretation	✓	✓	✓						
2a	Control Arm	✓	✓		✓					
2b	Substitution (Late Phase Trials)	✓	✓		✓					
3	Precision Powering								✓	
4	Inclusion/exclusion Criteria Optimization		✓							
5	Disease Modeling Capabilities								✓	
6	Improved Understanding of Geographic Differences	✓	✓							
7	Biomarker Development	✓	✓	✓						✓

Control Arm Substitution

Part or all of the control arm for the study can be comprised of historical data that could be pulled from the database (and/or elsewhere)

PSoC Data Sharing Initiative Overview
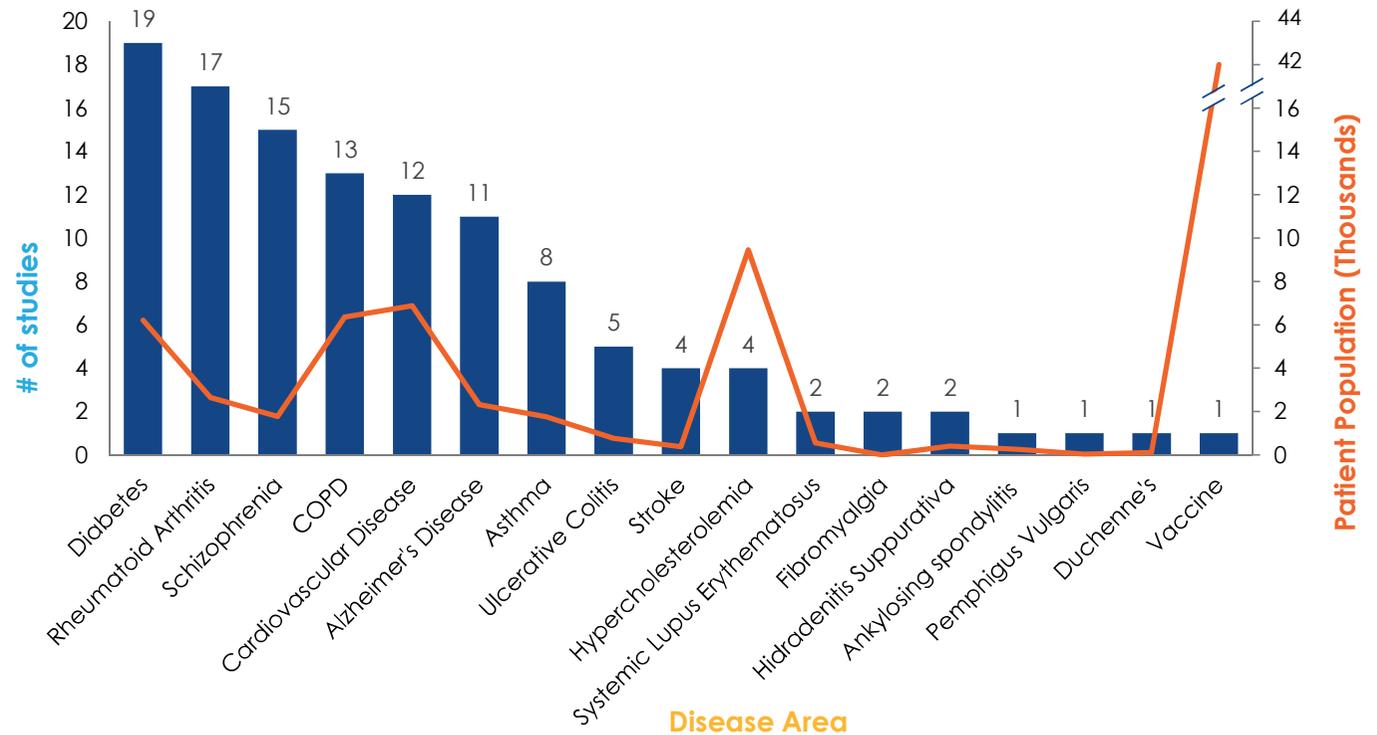*As of 27, June 2018*

118* Clinical Trials Shared

19 Disease Areas

82,419 Patients

Current Database Metrics

PSoC Multi-Stakeholder Workshop
Using historical data to accelerate confirmatory clinical trials

Health Authorities Engagement

Key challenges identified:

- **Controlling bias** in the trial population and in **appropriate selection** of data to use as a historical control
- Understanding **traceability challenges** around maintaining integrity and quality of the original source data

Public Multi-Stakeholder Workshop

May 15, 2018

Bethesda, MD

Attendees:

- Health Authorities
- Academia
- Patient Advocates
- Industry

Workshop Outcomes

- Create series of **best practices/ publications**
- **Explore new solutions** in feasibility pilots
- Sponsors encouraged to **submit to PDUFA VI** Complex Innovative Design Pilot Program
- **Continue engagement** with health authorities and key stakeholders (e.g. academia)

Manuscript

Minimizing Patient Burden through the Use of Historical Subject-Level Data in Innovative Confirmatory Clinical Trials

THERAPEUTIC INNOVATION & REGULATORY SCIENCE

Official Journal of DIA

DIA TIRS 2018

Click here to access Manuscript

There is a **sense of urgency** in developing medicines for patients in need

Regulators have a record of **accepting historical control data** for interventions for medical devices and/or indications with very small populations

The methods covered in this paper give us the tools to use fewer subjects in late-phase confirmatory clinical trials. **Bayesian** and **frequentist approaches** are outlined including how the operating characteristics for such a trial can be obtained. **Examples of approved new treatments** that **incorporated historical controls** in their **confirmatory trials** are presented

Industry & regulatory science has matured to the point where **high quality data exists** to support these approaches; the **statistical methods have evolved** to provide a robust understanding of risk; & our evolution to a patient-centric model demands that we **leverage these methods more broadly**

# One Proposed Approach for Using Historical Control Data in Confirmatory Trials

Prospective selection	Choose relevant controls	Robust prior *	Adaptive design
Historical trials should be carefully selected prospectively to **reduce any systematic differences** (trial conduct/design, changes in SOC over time, etc) between the current and historical trials in order to reduce the risk of bias.	If necessary (e.g. to adjust for differences between historical and current trials in inc/exc criteria, or in order to reduce the size of the historical data to prevent it overwhelming the concurrent data), **use a method such as propensity score matching to quantitatively identify the most relevant subset of historical control subjects**. This will build confidence that the historical prior is appropriate.	**Incorporate the subjects from step 2 into a robust prior** that down weights the influence of the historical control data when it is discordant with the concurrent control data. *Note that this is just one proposed Bayesian approach, but frequentist methods could also be used.*	Finally, where feasible, **use an adaptive trial design with an interim analysis to assess the comparability of the historical control data** to the concurrent control. If they are not comparable then additional control subjects would be included in the study. If they are comparable then the number of control subjects would not increase.

Incorporation of Historical Control Data Using Bayesian Priors: Benefits and Risks

Total # concurrent controls needed to achieve effective control N=200 when combined with historical controls

Historical response=0.65
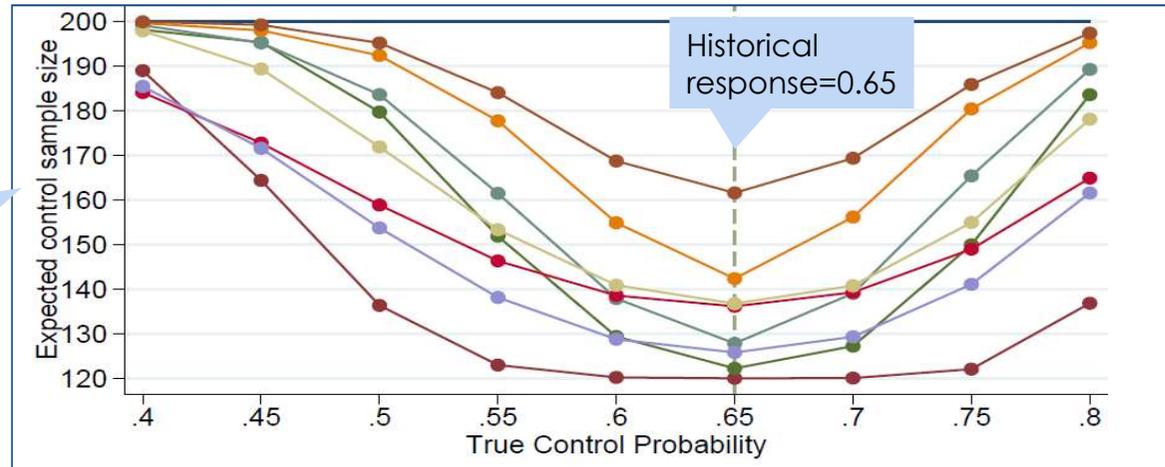
Ignore Historical
Robust MAP prior with 0.5*Be(1,1)
Equivalence prob weight (± 0.08)
Power prior with $\pi(\alpha_0) \sim$ Be(0.1,0.1)
Commensurate power, $\tau \sim$ Ga(0.001,0.001)
Robust MAP prior with 0.1*Be(1,1)
Probability weight
Power prior with $\pi(\alpha_0) \sim$ Be(0.4,0.4)
Commensurate power, $\tau \sim$ Ga(1,0.01)
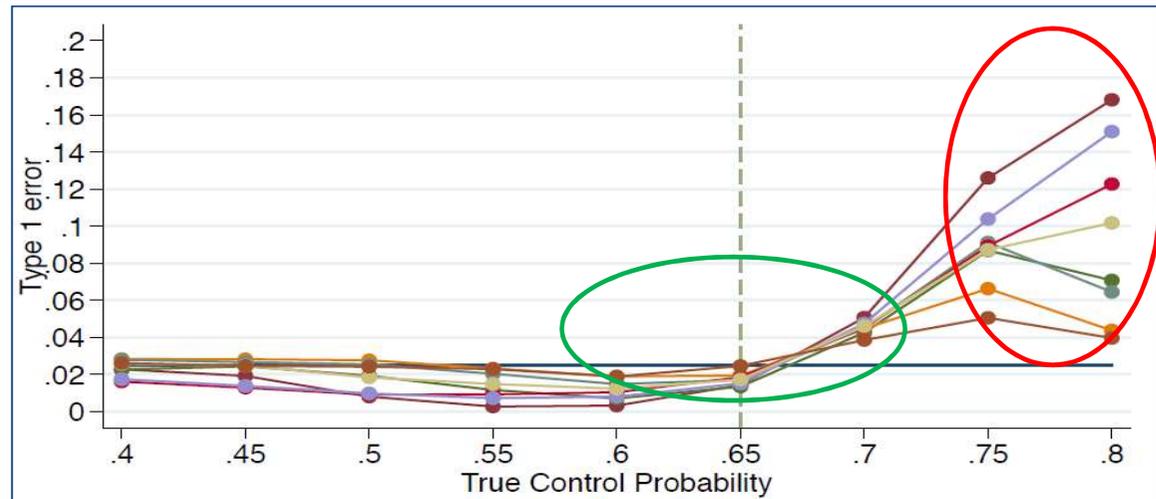
Maxine Bennett, MRC
Biostatistics Unit, UK
(Unpublished results)

Example: Supplement safety data in control arm with data from another trial by same sponsor

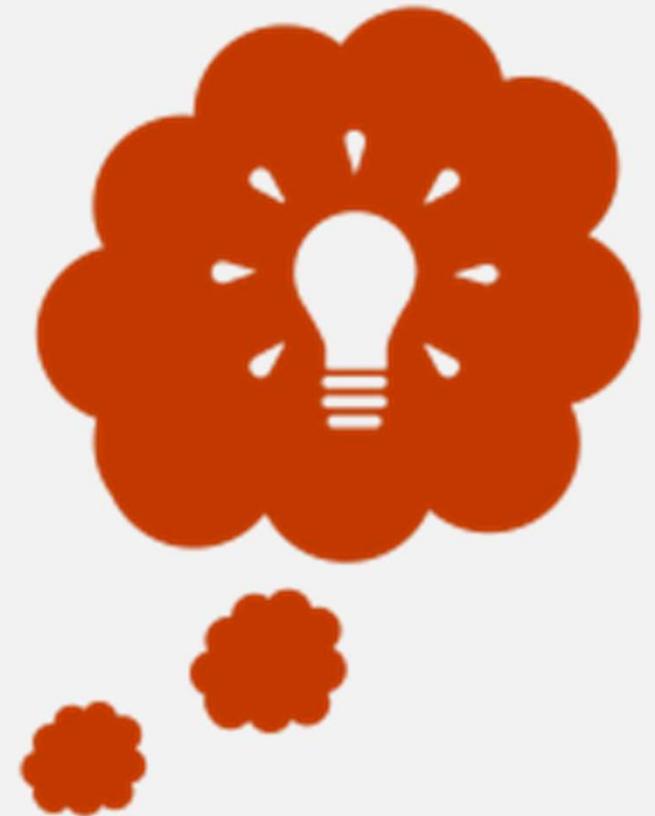| Trial A	• Very large Ph III trial of extended duration that is designed to demonstrate the safety of the once a day regimen of Drug X. • 1:1 randomization Drug X:SOC	**To demonstrate safety of Drug X in Trial B when given less frequently**
Trial B	• Single confirmatory trial that is designed to demonstrate the efficacy and safety of a less frequent regimen of Drug X. • 2:1 randomization Drug X:SOC	• Use information in Trial B on SOC from Trial A through the use of a Bayesian framework (dynamic borrowing using two approaches: commensurate prior and robust mixture prior)

Conclusion

"All the forces in the world are not so powerful as an idea whose time has come."

- Victor Hugo

Q&A