Shortening the Timeline for Developing New Treatments

How the Rare Disease Cures Accelerator – Data and Analytics Platform (RDCA-DAP) Can Help

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Alone we are rare. Together we are strong.
Agenda

Opening
Alexa Moore, NORD

Speakers
Pamela Gavin, NORD
Michelle Campbell, FDA/CDER
Jane Larkindale, C-Path
Robert Alexander, Takeda

Q&A
All Panelists
Shortening the Timeline for Developing New Treatments – How the Rare Disease Cures Accelerator – Data and Analytics Platform (RDCA-DAP) Can Help

Pamela Gavin, MBA
Chief Strategy Officer, National Organization for Rare Disorders

Michelle Campbell, PhD
Sr. Clinical Analyst, Stakeholder Engagement and Clinical Outcomes, Office of Neuroscience, FDA/CDER

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Executive Director, Rare Disease Cures Accelerator-Data and Analytics Platform and Duchenne Regulatory Science Consortium, C-Path

Robert Alexander, MD
Vice President and Head, Global Clinical Science Neuroscience Therapeutic Area Unit, Takeda Pharmaceuticals International Co.
Pamela Gavin, MBA
Chief Strategy Officer, NORD
HOW DOES THE ORPHAN DRUG ACT WORK?

There are 4 INCENTIVES in the law that encourage biopharmaceutical companies to develop orphan drugs.

- 7 YEARS OF EXCLUSIVITY that prevent competitors from selling the same product labeled for the orphan indication.
- 25% TAX CREDIT for qualified clinical testing expenses incurred in clinical trials.
- ~$18 MILLION in FDA research grant funding.
- ~$2.5 MILLION FDA user fees waived.
Orphan Drug Act Successes

48 Novel Drugs Approved by CDER in 2019

27 Non-orphan products
21 Orphan products

Nearly 44% were orphan products

Number of approved orphan indications per year

1983 2016 2017 2018 2019
2 40 82 90 75
Rare Disease Landscape

There are over 7,000 rare diseases. More than 90% of rare diseases are without an FDA-approved treatment. Many rare diseases aren’t being studied.
Rare Challenges

Expense/Limited funding for the study of rare diseases
Impacts scientific discovery, the development of expertise

Limited understanding of progression of many rare diseases
Over time and for different people
Impacts drug development interest, duration of development, design of clinical trials

Small patient populations spread over diverse geographic area
Challenges clinical trial design and recruitment
Harder to detect and understand effects

Standardization of data and measures
Challenges the ability to combine and compare
Can shape quality, utility, and interpretation of data

Data ownership and sharing
Restricted ownership
Multiple studies, same condition
Split already small communities across multiple efforts (increasing burden on participants)
The RDCA-DAP is a neutral, independent integrated database and analytics hub designed to be used in building novel tools to accelerate drug development across rare diseases.

- **Promotes sharing of patient level data**
- **Encourages standardization of data collection**
- **Allows access to the data by researchers (as permitted by contributor)**
- **Better understanding of a rare disease and its progression**
RDCA-DAP Benefits

- **360° view** of disease characterization and natural history
- **Accelerate understanding** of conditions and commercial/research interest; inform the design of trials
- **Encourage greater representativeness** in study samples - steps toward more equitable and inclusive study designs
- **Opportunity** for cross-disease discovery
- **Efficient, effective** use of resources
Rare Disease Cures Accelerator-Data and Analytics Platform

Michelle Campbell, PhD
Sr. Clinical Analyst, Stakeholder Engagement and Clinical Outcomes Office of Neuroscience
FDA/CDER
Context and Motivation

• Regulators are working with rare disease patients, investigators, and companies, mostly one at a time, and most struggling with the same challenges:

  • Vast knowledge gaps about the natural course of the disease and small dispersed patient populations that make it hard to do the randomized clinical trials that save lives.

• There is a need for a better solution.
# Key activities presenting areas of challenge

<table>
<thead>
<tr>
<th>Discovery / Translational / Preclinical</th>
<th>Clinical Development</th>
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</thead>
<tbody>
<tr>
<td><strong>Characterization of Disease</strong></td>
<td><strong>Clinical Study of New Treatments</strong></td>
</tr>
<tr>
<td>• What is known about the disease?</td>
<td>• Is the investigational drug available in a form that can be administered?</td>
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<tr>
<td>• Are there well-defined lab tests—to diagnose the disease?</td>
<td>• Pre-clinical safety testing done to inform assessment of safety in humans?</td>
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<tr>
<td>• What is the natural history of the disease?</td>
<td>• A study design specified?</td>
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<tr>
<td>• What causes the disease (pathogenesis)?</td>
<td>• A study protocol?</td>
</tr>
<tr>
<td><strong>Getting Patient Perspectives on their Disease and Treatment</strong></td>
<td>• IRB review and approval?</td>
</tr>
<tr>
<td>• What disease impacts matter most to patients?</td>
<td>• IND submitted for FDA review?</td>
</tr>
<tr>
<td>• What is the landscape of currently available treatments?</td>
<td>• Plan for patient enrollment?</td>
</tr>
<tr>
<td></td>
<td>• Patient access to the trial site?</td>
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<tr>
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<td>• Plan for study data collection?</td>
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Congress provided FDA an Opportunity in its Fiscal Year 2019 Appropriation

Within the increases provided for a New Platform for Drug Development in FY 2019, Congress appropriated funding for Investment and Innovation for Rare Diseases

CDER is investing funds in Innovation for Rare Diseases to launch work on “Rare Disease Cures Accelerator.”
Need for a “Rare Disease Cures Accelerator”

- Adopting a cooperative research approach to accelerate the move from bench to bedside for rare disease cures.

- A “Rare Disease Cures Accelerator” would provide the infrastructure for a cooperative scientific approach to clinical trials readiness in rare diseases.

- Some key components include:
  - Centralized standardized infrastructure to support and accelerate rare disease characterization
  - Standard core sets of COAs measuring impacts that matter most to patients, ideally applicable to more than one rare disease
  - Global rare disease clinical trials network
Centralized standardized infrastructure to support and accelerate rare disease characterization

- There is a compelling need for:
  - Efficient comprehensive characterization of the natural history of a given rare disease targeted for clinical development
  - Characterization conducted rigorously with attention to established data quality standards, in order to be most useful to clinical trial design and regulatory review

- A standardized rare disease natural history study data platform is needed to provide a sustainable approach
  - This platform would provide a disease-neutral background data framework for the conduct of standardized natural history studies.
  - Disease-specific needs would be layered onto this framework to provide a rapid means for standardized, yet customized, development of natural history studies for any given disease.
The Rare Disease Cures Accelerator- Data and Analytics Platform (RDCA-DAP) is intended to serve as a neutral, independent data collaboration and analytics hub to promote the sharing of critically important data across rare diseases in order to accelerate the understanding of disease progression.
RDCA-DAP

Critical Path Institute and NORD partnering on initiative
RDCA-DAP: Long-term goal for impact on drug development

• Centralized and standardized infrastructure to support and accelerate rare disease characterization, allowing development of more efficient and effective clinical trial protocols

• Standardized data that can be extracted in CDISC format for regulatory submissions

• Aggregated data will allow for a better understanding of the variance in disease progression across broad range of patients aiding in development of optimized clinical trial protocols (endpoints, inclusion criteria, length and size of trial)

• Analytics and simulation tools to help optimize your trial protocol for your therapy

• Ability to look at dynamics of change in outcome measures and biomarkers in individual disease states and in related diseases and understand sources of variation in rate of change.

• Ability to potentially find and match historical or contemporary control patients to enrich your placebo arm and reduce numbers of patients.
How do we add data to the RDCA-DAP, and what do we get out of it?

Jane Larkindale, DPhil
Executive Director, RDCA-DAP
Interacting with RDCA-DAP

Where does data come from?
- Clinical Trial Data
- Registry Data
- Natural History Data
- Genomic Data
- Imaging Data
- Surveillance Data
- Preclinical Data
- Other Novel Data

What do you do with the data?
- Curation
- Incoming Data Storage
- Standardization
- Integrated Data for Analysis

C-Path Online Data Repository

How can I see and use the data?
- Interface level I: Dashboard
- Interface level II: Data interrogator and data
- Interface level III: Advanced analytics
RDCA-DAP – Where does the data come from?

- RDCA-DAP does not collect new data from patients or in new studies
- RDCA-DAP seeks to get copies of data from existing sources:
  - Clinical trial data [Baseline, Placebo arm and Drug arm all have value!]
  - Natural history data
  - Registries (patient-entered, clinical, etc.)
  - Other sources
- You cannot identify any individual in RDCA-DAP’s data
- Data from multiple sources is integrated
Why share data?

• Because shared data can be aggregated into bigger datasets with increased power and predictivity

• Because larger datasets reflect broader groups of patients and can be more representative of the whole population and help develop more informative trials

• Because it will help inform us on how to collect better data and more useful data in the future and develop well-designed fit-for-purpose measures

• Because the data can be used for so many different things that we will be able to generate deep learning within and across diseases
Data sharing concerns from industry

- Will others re-analyze my data and come to different conclusions?
- Will regulators look at this data and come to new conclusions about my therapy?
- No one else can really understand my data. There are people out there who may publish poor analyses of this data.
- I will lose competitive advantage over other companies
Clinical data contributed to C-Path

Number of Clinical Subjects

Cumulative Number of Patients Received

- Alzheimer's Disease
- Duchenne Muscular Dystrophy
- Friedreich's Ataxia
- Healthy Kidney Study
- Huntington's Disease
- Multiple Sclerosis
- Parkinson's Disease
- Polycystic Kidney Disease
- Transplant Therapeutics
- Type 1 Diabetes
- Tuberculosis

Types of data:
- Alzheimer's Disease
- Duchenne Muscular Dystrophy
- Friedreich's Ataxia
- Healthy Kidney Study
- Huntington's Disease
- Multiple Sclerosis
- Parkinson's Disease
- Polycystic Kidney Disease
- Transplant Therapeutics
- Type 1 Diabetes
- Tuberculosis

Cumulative Number of Patients Received

- 2010/06
- 2011/06
- 2012/06
- 2013/06
- 2014/06
- 2015/06
- 2016/06
- 2017/06
- 2018/06
- 2019/06
- 2020/01

- 0
- 20,000
- 40,000
- 60,000
- 80,000
- 100,000
- 120,000

- 100,000
- 110,000
- 120,000
Process for incoming data

**INPUT**
- Clinical Trial Data
- Natural History Data
- Patient Registry
- Clinical Data
- Other Data

**C-PATH OUTPUT**
- Tools and analysis developed with data made available
- Data available per custodian’s direction
RDCA-DAP will also improve future data collection

**INPUT**
- Clinical Trial Data
- Natural History Data
- Patient Registry
- Clinical Data
- Other Data

**C-PATH PROCESS**
- RDCA-DAP contact with custodian, negotiate data sharing agreement
- Data transfer
- Data exploration and mapping

**C-PATH OUTPUT**
- Feedback to custodians on data gaps, gaps in standardization, other enhancements to collection
- Standardized data returned to custodians
- Analysis and tools available
- Larger dataset available

Tools and analysis developed with data made available
Data available per custodian’s direction
Drug development tools that can be built from integrated data

**Biomarkers:** Total Kidney Volume (TKV) qualified as a prognostic biomarker for polycystic kidney disease (PKD), now accepted as a reasonably likely surrogate endpoint.

**Models:** Clinical trial enrichment tool for Parkinson’s Disease.

**Endpoints:** Understanding variability in Duchenne progression as measured by different endpoints.

PD trial power with and without enrichment – 25% reduction in trial size.
Clinical Trial Simulation

Trial design parameters:
- Study duration
- Assessment frequency

Baseline Patient features:
- FVC
- Age
- Race
- del 3-7/skip-44 mutation

Assumed drug effects:
- % changes to model parameters to mimic drug effects
- Adjustable times to effect

Plotting window by user chosen time metric:
- Plots by age groups
- Plots by time in study
- Provides mouse-over quantitative values

Number of trials to simulate
Simulation output export feature:
- Export virtual patient data
- Export plots
- Export power estimates

Thanks to the Duchenne Regulatory Science Consortium; in particular Sarah Kim, Karthik Linguneni and Francesco Morales from the University of Florida.
Interacting with RDCA-DAP

RDCA-DAP DATA COLLABORATION CENTER

Data Vault → Curation → Incoming Data Storage → Standardization → Integrated Data for Analysis

C-Path Online Data Repository

User Friendly, Secure Cloud Interface

Interface level I: Dashboard

Interface level II: Data interrogator and

Interface level III: Advanced analytics

ACTIONABLE DRUG DEVELOPMENT SOLUTIONS

Clinical Trial Data
Registry Data
Natural History Data
Genomic Data
Imaging Data
Surveillance Data
Preclinical Data
Other Novel Data

#RDCADAP
RDCA-DAP will:

• Provide curated and standardized rare disease data to companies and other researchers

• Allow cross disease searches to inform us on how best to develop drugs in new disease areas

• Help the rare disease community improve data collection and data analysis over time

• Provide an analytics platform to help use data to accelerate drug development [target discovery, biomarker discovery, clinical trial optimization...]

• Help make drug development efficient and effective for rare diseases
Sharing the TOMMORROW study results

RDCA-DAP Webinar

June 24, 2020

Robert Alexander, MD
Takeda Development Center Americas, Inc., Cambridge, MA, USA
The TOMMORROW STUDY was supported by the Takeda Pharmaceutical Company.

The work was conducted as part of a business alliance with Zinfandel Pharmaceuticals, Inc., Chapel Hill, NC, USA.

Robert Alexander, MD: full-time employee of Takeda.
Study Overview

The TOMMORROW study was designed to pursue two primary objectives independently yet simultaneously:

1. To prospectively qualify a biomarker risk algorithm (BRAA) comprised of TOMM40 rs10524523 genotype, APOE genotype, and age as a biomarker for prognosis of an individual’s risk of developing MCI due to AD in the next 5 years

and

2. To evaluate the efficacy of a low dose of pioglitazone to delay the onset of MCI due to AD in cognitively normal subjects who were classified by the algorithm to be at high risk of developing MCI due to AD within 5 years

AD, Alzheimer’s disease; APOE, apolipoprotein E; MCI, mild cognitive impairment.
TOMMORROW Study: Phase 3 Study Schematic

Screening

Double-Blind Treatment

Follow-Up

Single global registration trial

High risk

Placebo (N = 1,516)

Pioglitazone 0.8 mg SR (N = 1,545)

Low risk

Placebo (N = 433)

24,136 in US, EU, AU (all-comers)

3494 cognitively normal participants (65–83 years of age) and their project partners

Co-primary endpoints
(time-to-event)

Efficacy

BRAA Qualification

A target of 202 Primary Endpoint Events

Duration = event-driven (anticipated ~5 years)
(PE event = adjudicated MCI due to AD)

BRAA, biomarker risk assignment algorithm; SR, sustained release.
Study was terminated due to efficacy futility prior to completion

- Jul 24: treatment effect size ↑ from 30% to 40%
- Aug 28: first subject in
- Dec 22: last subject in
- Jan 05: efficacy futility analysis*
- Aug 07: last subject out
- Oct 24: Topline results (CTAD)
- Jan 31: study termination

*Threshold set at 30% conditional probability that a 40% treatment difference would be detected at the end of the study.

CTAD, Clinical Trials on Alzheimer's Disease.
Subject Disposition (All Subjects)

Mean exposure duration = 31.8 months  
*(Planned study duration ~ 60 months)*
**BRAA: Time to MCI Due to AD**  
(Full Analysis Set, Non-Hispanic/Latino Caucasians)

<table>
<thead>
<tr>
<th></th>
<th>Low-Risk Placebo (N=402)</th>
<th>High-Risk Placebo (N=1406)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Events (%)</td>
<td>4 (1.0)</td>
<td>46 (3.3)</td>
</tr>
<tr>
<td>Total Censored (%)</td>
<td>398 (99.0)</td>
<td>1360 (96.7)</td>
</tr>
<tr>
<td>Median Time to Event (Days)</td>
<td>634</td>
<td>383</td>
</tr>
<tr>
<td>Hazard Ratio, High vs. Low (99% CI)</td>
<td>3.26 (0.85, 12.45)</td>
<td></td>
</tr>
<tr>
<td>P-value, Hazard Ratio</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>P-value from Sensitivity Analysis 1</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>P-value from Sensitivity Analysis 2</td>
<td>0.015</td>
<td></td>
</tr>
</tbody>
</table>

- Randomized subjects who took at least one dose of study drug.
- The hazard ratio and its p-value were obtained from the proportional hazards model with terms for center, gender, and education, against level of statistical significance at 0.01.
- Obtained using a nonparametric analysis accounting for interval censoring.
- Obtained using a nonparametric analysis (log-rank test) stratified by gender.
Pioglitazone: Time to MCI Due to AD (Full Analysis Set, Non-Hispanic/Latino Caucasians)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>High-Risk Placebo (N=1406)</th>
<th>High-Risk Pioglitazone 0.8 mg (N=1430)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Events (%)</td>
<td>46 (3.3)</td>
<td>39 (2.7)</td>
</tr>
<tr>
<td>Total Censored (%)</td>
<td>1360 (96.7)</td>
<td>1391 (97.3)</td>
</tr>
<tr>
<td>Median Time to Event (Days)</td>
<td>383</td>
<td>372</td>
</tr>
<tr>
<td>Hazard Ratio, Pioglitazone vs. Placebo (99% CI) (^b)</td>
<td>0.80 (0.45, 1.40)</td>
<td></td>
</tr>
<tr>
<td>P-value, Adjusted Risk ratio (^b)</td>
<td>0.307</td>
<td></td>
</tr>
<tr>
<td>P-value from Sensitivity Analysis 1 (^c)</td>
<td>0.314</td>
<td></td>
</tr>
<tr>
<td>P-value from Sensitivity Analysis 2 (^d)</td>
<td>0.315</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Randomized subjects who took at least one dose of study drug.
\(^b\)The hazard ratio and its \(p\)-value were obtained from the proportional hazards model with terms for center, gender, education and age (continuous), against level of statistical significance at 0.01.
\(^c\)Obtained using a nonparametric analysis accounting for interval censoring.
\(^d\)Obtained using a nonparametric analysis (log-rank test) stratified by gender.
SAEs and AEs of Special Interest (Safety Set)*

*Randomized subjects who took at least one dose of study drug.
## Treatment-Emergent Adverse Events (Safety Set)*

<table>
<thead>
<tr>
<th></th>
<th>Low-Risk Placebo (N=427)</th>
<th>High-Risk Placebo (N=1507)</th>
<th>High-Risk Pioglitazone 0.8 mg (N=1531)</th>
<th>Overall (N=3465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With any TEAE</td>
<td>379 (88.8%)</td>
<td>1320 (87.6%)</td>
<td>1361 (88.9%)</td>
<td>3060 (88.3%)</td>
</tr>
<tr>
<td>TEAE leads to study drug discontinuation</td>
<td>37 (8.7%)</td>
<td>164 (10.9%)</td>
<td>131 (8.6%)</td>
<td>332 (9.6%)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>81 (19.0%)</td>
<td>404 (26.8%)</td>
<td>358 (23.4%)</td>
<td>843 (24.3%)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (0.5%)</td>
<td><strong>21 (1.4%)</strong></td>
<td>7 (0.5%)</td>
<td>30 (0.9%)</td>
</tr>
</tbody>
</table>

*Randomized subjects who took at least one dose of study drug. TEAE, treatment-emergent adverse event.
Summary

• Study accumulated a total of 96 adjudicated primary endpoint events of MCI due to AD
• Study was terminated prior to completion due to prespecified efficacy futility analysis
• For primary endpoints:
  – Biomarker risk algorithm: Hazard ratio (high risk vs low risk, 99% CI) = 3.26 (0.85, 12.45); p-value=0.023
    ◦ BRAA was generally successful at enriching the study for those at high risk of developing MCI due to AD
  – Pioglitazone SR 0.8 mg: Hazard ratio (pioglitazone vs placebo, 99% CI) = 0.8 (0.45, 1.4); p-value=0.307
    ◦ Subgroup analysis indicated a possible benefit in men
• MCI due to AD converter profile
  – Imputation of amyloid using MRI showed most converters were amyloid positive
• Safety
  – Pioglitazone SR 0.8 mg was safe and well tolerated in the study
  – A lower percentage of high-risk pioglitazone-treated subjects experienced death compared with high-risk placebo-treated subjects, primarily due to fewer CV deaths
TOMMORROW Study Data Sharing

Developing large cross-study data-set for regulators to access

Curated data mapped to common standards – will manage long-term governance

Takeda Policy sharing
Sharing Study Data – Pharma Perspective

- Takeda is committed to data transparency (core values) and we see great value in curation, harmonization and aggregation of disease-specific pivotal data-sets
  - Lessens the burden of curation, harmonization and aggregation on the part of the researcher
  - We see this as an important complement to data sharing registers like Vivli.org

- Data sharing requires an internal champion
  - Once a study is over, resources have been moved to new projects – data sharing is “no one’s job”
  - Someone needs to keep process moving and overcome roadblocks

- The TOMMORROW study represents an easier case:
  - Study was negative and project was terminated
  - Drug is off patent

- But still, there were concerns:
  - Could safety data be misinterpreted?
  - Is the company losing out on important IP?
Some issues for our lawyers

- Critical Path was very receptive to our input
- The original CPAD data contribution agreement (DCA) had text that seemed in some cases restrictive and burdensome and this created a lot of edits.
  For example:
  - Sponsor had to attest that specific consents and IRB approvals were in place to explicitly permit this sharing [when in fact “legacy” consents are more general usually])
  - De-identification of data and privacy protections were not clear (HIPAA not sufficient for Takeda)
  - Other aspects of data use/terms of use were unclear (will data be downloaded by researchers?)
Summary and Recommendations

• Understanding why it is difficult for companies to share data is important.

• Fast-tracking key data could be facilitated if support for anonymization/de-identification support would be provided via a third-party.

• Data sharing repositories should consider privacy and rarity of disease in contribution agreements and modify approach accordingly (more fit for purpose DCA and research environment plans).
Acknowledgements

Thank you to the many study participants and their project partners at each site

- Site investigators, neuropsychologists, staff (US, GB, AU, DE, CH)

- TOMMORROW neuropsychology science
  - Neuropsychology advisory board, Neuropsychology Lead Office

- TOMMORROW external committees
  - Data safety monitoring board, adjudication committee, external advisory committee

- TOMMORROW vendor partners

- TOMMORROW (Takeda/Zinfandel) alliance team
Questions?
Please enter your questions in chat.

Further information is at: c-path.org/programs/rdca-dap/
To contribute data contact: rdcadap@c-path.org
We want to hear from you!

Are you ready to join this collective effort to find tomorrow’s treatments today?

If you are ready to contribute data now, visit c-path.org/programs/rdca-dap/ or email rdcadap@c-path.org to start a conversation.
RDCA-DAP Virtual Workshop

SAVE THE DATE
October 19, 2020

Registration is NOW open: https://bit.ly/RDCADAPWORKSHOP2020