A roadmap for real-world evidence generation in Alzheimer's disease

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Introduction

The purpose of this white paper is to describe Biogen's ongoing commitment to further characterize the safety and effectiveness of treatments for neurological disorders such as Alzheimer's disease as they become part of routine clinical practice in the United States (U.S.). The need for and importance of real-world evidence (RWE) is highlighted as a complement to randomized clinical trial (RCT) data, while building diversity goals for both. Biogen's ongoing and planned evidence generation efforts to optimize the clinical and payer community's understanding of the safety and effectiveness of treatments in routine clinical practice are described. As articulated below, in addition to a post-marketing commitment RCT, Biogen intends to use a variety of real-world data sources including claims and billing activities, product and disease registries, and patient-generated data including those captured in home-use settings.

Background

For regulatory approval purposes, RCTs have long been considered the gold standard to estimate the effectiveness of a new intervention or treatment. Homogeneity of the patient population is often desired in these registration trials to minimize variance introduced by patient and disease characteristics associated with the efficacy and safety outcomes of care (e.g., comorbid conditions).[1] Together, randomization, blinding, and homogeneity in the trial patient population reduces bias and provides a rigorous tool to examine cause-effect relationships between an intervention and outcome in a relatively homogeneous patient population.[2] A common limitation of RCT data is that the results obtained in a well-controlled setting for a relatively homogeneous patient population may not be representative of or generalizable to the target patient population.

Accelerated approval[3] is intended to provide earlier access to drugs for serious diseases when there is residual uncertainty from RCT evidence collected at the time of approval regarding the drug's ultimate clinical benefit. Accelerated approval is permitted when 4 requirements are met: (1) the drug must be for treatment of a serious disease with unmet medical needs; (2) the drug must be expected to provide meaningful clinical advantage over available therapy; (3) there must be a showing of an effect of the drug on a surrogate end point (typically, that reflects the underlying pathology of the disease); and (4) there must be a determination that it is reasonably likely that the effect on the surrogate end point predicts clinical benefit of the drug.

A multiple myeloma case study cited by Pharmaceutical Research and Manufacturers of America (PhRMA) in a report on accelerated approval illustrates the impact accelerated approval can have on patient outcomes.[4] It notes that 10 medicines for multiple myeloma have been granted accelerated approval and "the average life expectancy for [this] common hematological malignancy is now anywhere between 8-10 years, when prior, it was about two years"; attributing that the observed improvement was "greatly due to drugs that were approved under accelerated approval."[4] The majority of these approvals were based on response rate or time to progression, rather than overall survival and these advancements in treatment have led to a nearly 90% increase in 5-year survival rates compared to the 1990s.[5,6] In sum, ensuring earlier patient access to these treatments via an accelerated approval pathway benefited many patients who would otherwise have waited years for a traditional FDA approval of these medicines.

The value of real-world evidence generation in Alzheimer's disease as a complement to randomized clinical trial data

Following any approval, but particularly valuable following accelerated approval, the collection of RWE serves as the next step in the evidence continuum. RWE complements RCT data as a means to fully understand the patient journey; as well as evaluate drug effectiveness, safety, and value as part of routine clinical practice.

The FDA describes RWE as clinical evidence on the usage and potential benefits and risks of a drug derived from real-world data, which are data related to patient health status or the delivery of health care routinely collected outside the scope of RCTs, including electronic health records, claims, registries, and patient-generated data.[7,8]

Over the past decade, there has been increased recognition of the value of RWE collection post FDA-approval as a means to inform patient access, effectiveness, safety, and appropriate use.[7,9] The 21st Century Cures Act (Cures Act), signed into law on December 13, 2016, was designed to accelerate medical product development and bring new innovations and advances more quickly and efficiently to the patients who need them.[9,10,11] The Cures 2.0 Act introduced on November 15, 2021, includes the provision for the use of RWE in the evaluation of the safety and effectiveness of drugs and biologics after FDA approval.[12,13]

RWE has also been used to supplement phase 3 registration trial data, understand the patient journey, and assess drug safety and effectiveness in the real-world in a variety of therapeutic areas. Perhaps the most publicly visible example of the added value of RWE can

be found in the ongoing efficacy and safety evaluations of the coronavirus disease 2019 (COVID-19) vaccines. Within months of FDA approval, a Centers for Disease Control and Prevention (CDC) study using data from a network covering 500,000 health care professionals across 33 sites in 25 U.S. states reported robust evidence that messenger ribonucleic acid (mRNA) vaccines are safe and effective against symptomatic illness in real-world settings – demonstrating their value in record time, accelerating adoption, and saving countless lives.[14]

Another great example of leveraging real-world data to generate critical information for expediting learning in real time and enabling decision making is the Cystic Fibrosis (CF) Foundation Patient Registry. Although CF is a rare disease, the principle of leveraging RWE to inform appropriate use in routine clinical care applies. This registry collects information on the health status of people with CF who receive care in CF Foundation-accredited care centers and agree to participate in the registry. The RWE generated is used to create CF care guidelines, assist care teams providing care to individuals with CF, and guide quality improvement initiatives at care centers. Researchers also use the patient registry to study CF treatments and outcomes, and to design CF clinical trials.[15]

In line with the principles outlined in 2018 by senior officials from the FDA, CMS, National Institutes of Health (NIH), and other health agencies, Biogen strongly supports real-world data collection initiatives for Alzheimer's disease.[9] There are several inherent benefits to this type of data collection within the Alzheimer's disease community.

Data from RWE are observational and are often routinely collected as standard of care. Thus, their collection presents a lower burden on patients, caregivers, and healthcare providers which is particularly relevant in the area of Alzheimer's disease, where a key objective of patient care should be alleviating the day-to-day burden on patients and caregivers.

Additionally, real-world studies include larger patient populations that are historically underrepresented in randomized controlled trials (e.g., patients who are ethnically/racially/geographically diverse, have comorbid conditions, are taking concomitant medications) and thus help mitigate any potential generalizability issues that impact RCTs.[16]

The Alzheimer's Association, the American College of Radiology, the American Society of Neuroradiology, and the Department of Biostatistics, Brown University School of Public Health, along with other clinical research experts, have announced a national registry, The National Treatment and Diagnostic Alzheimer's Registry (ALZ-NET). This new national

registry will be an FDA-approved-agent agnostic approach to gathering routine clinical practice data and outcomes for sharing quickly and transparently with all stakeholders. Biogen is actively partnering with the Alzheimer's Association to develop and implement the registry.

Additionally, UsAgainstAlzheimer is proposing the creation of an Alzheimer's Disease Evidence Accelerator (ADEA) framework designed after the American Society of Clinical Oncology's (ASCO's) CancerLinQ initiative[17] and the recent COVID Evidence Accelerators with an aim of enabling a Learning Health System, which collects clinical data in real time for analysis that can be used by participating physicians to improve the quality and outcomes of care.

Biogen has significant experience generating meaningful RWE across multiple therapeutic areas. In 2021, Biogen generated multimodal RWE to inform the effectiveness and safety of nusinersen among patients with spinal muscular atrophy (SMA) type III and type IV.[18] This research helped the European Medicines Agency (EMA) inform medical practice and identify the appropriate patient population that would benefit the most from treatment with nusinersen, further establishing that RWE coupled with clinical trial data can be informative for establishing treatment effectiveness.[18,19]

Biogen's commitment to real-world evidence generation efforts in Alzheimer's disease

In early January 2022, CMS released a draft decision[20] that would only permit Medicare coverage for anti-amyloid monoclonal antibodies for the treatment of Alzheimer's disease for patients who are enrolled in qualifying clinical trials. As stated in Biogen's public comment letter to CMS dated February 10, 2022, Biogen continues to believe that the three-pronged post-approval RWE generation program described below will address the clinical, safety and care management issues (e.g., safety and effectiveness in diverse patient safety population) raised by CMS. By demonstrating the real-life generalizability of clinical trials results from EMERGE and ENGAGE, this RWE program will address the following key objectives:

- Utilizing well-established clinical and patient outcome assessments captured in International Collaboration for Real-World Evidence in Alzheimer's Disease (ICARE AD) and Clinical Data Research Network (CDRN), Biogen will investigate whether amyloid-directed monoclonal antibody therapies result in statistically and clinically meaningful difference in decline in cognition, function, and other Patient Reported Outcomes (PROs);

- In addition to the data collected in ICARE AD and CDRN, the CMS claims analysis will utilize clinical, diagnosis, and procedure codes to assess the frequency and clinical impact of adverse events associated with treatments;

- Through the collection of key clinical data and analysis of its impact on patient outcomes, ICARE AD and CDRN will examine whether reducing amyloid burden results in improved patient outcomes;

- Through the collection and analysis of cognition, function, and safety data, all three RWE approaches will elucidate the benefit/risk profile for key sub-populations of eligible patients;

- Finally, RWE generation affords the opportunity to evaluate the benefit/risk profile of treatment in a broad, diverse population that is more representative of the entire Alzheimer's disease community.

Biogen's commitment to patient diversity, equity, and inclusion in Real World Evidence generation efforts in Alzheimer's disease

Racial inequities in clinical trials are a problem for the entire industry, across therapeutic areas. Alzheimer's disease trials historically have struggled to enroll participants from the Black/African-American community – overall, trials have had an average of 2-3% representation. Biogen is aware that common barriers to participating in clinical trials include distrust of the health care system, inadequate information about research and opportunities to participate, access to sites and specialists, and logistical concerns.

Over the last year, the emphasis on RWE generation in Alzheimer's disease has grown, with patient advocacy groups (PAGs) announcing the need to accelerate, advance, and identify gaps in effectiveness and safety through RWE, with a focus on generating data in diverse patient populations.[21,22] More specifically, real-world studies can provide key information and insights on the following aspects that cannot be generated in the clinical trial setting:

- Holistic understanding of treatment- and disease-related outcomes (e.g., comorbidities) in a much larger patient population with a more demographically and clinically diverse profile.

- Understanding of patient, family, and caregiver benefits that contribute to the clinical meaningfulness of treatments through assessing patient-centric outcomes such as

quality of life, caregiver/partner burden, and patient and care partner global impression of health.

- Characterization of the long-term impact of new, potentially disease-modifying therapies on the patient journey, standard of care, and monitoring approaches in routine clinical practice.

- Adherence to dosing and safety monitoring protocols (e.g., dose titration per label and use of magnetic resonance imaging [MRI] to monitor for amyloid-related imaging abnormalities [ARIA]).

To optimize evidence generation efforts, real world studies would benefit from improved coding in the International Classification of Diseases (ICD) so that clinicians can be specific in their reporting on the patient journey with Alzheimer's disease. The National Minority Quality Forum (NMQF) has already started that process by successfully bringing together a team of clinicians, patient advocates, and industry partners to expand ICD-10-CM coding for stages of severity of Alzheimer's disease and neuropsychiatric symptoms of dementia. This ongoing work is performed under the aegis of NMQF's National Alliance for Brain Health and Awareness.

A final important piece of background information to fully understand Biogen's evidence generation agenda is the commitment to actively seek solutions to address health inequities faced by underserved and underrepresented populations in clinical research, particularly in Alzheimer's disease. Like most RCTs, the generalizability of Biogen's pivotal trials to the target patient population is impacted by the lack of adequate diversity – that is, the number of Black/African American and Hispanic population in these trials were not representative of the Alzheimer's disease community. Therefore, building diversity goals into real-world studies will allow us to explore drug effectiveness, safety, and value in people underrepresented in RCTs, and provide insights into the appropriate benefit/risk-management strategies for different population groups, including different race and ethnic groups, and people with existing comorbidities.

As detailed below, Biogen have committed to specific diversity goals for the confirmatory, Post-Marketing Requirement (PMR) ENVISION study and RWE initiatives such as ICARE Alzheimer's disease and the CDRN. To illustrate, in the ENVISION post-marketing confirmatory study, Biogen aims to enroll 18% of U.S. participants from Black/African American and Hispanic populations, and in the ICARE AD real world registry, Biogen has a goal of 16% of U.S. participants from Black/African American and Hispanic populations.

Biogen set this goal to match the diversity among Americans diagnosed with early Alzheimer's disease and are taking a more targeted and intentional approach to diverse enrollment across the RWE programs. There are three main strategies to meet these goals: 1) Biogen is selecting sites with diverse staff, located in communities of color and with access to diverse patient populations; 2) Biogen is actively supporting sites in the identification of outreach to and engagement with underrepresented communities; 3) Biogen will deploy tactics aimed at increasing Alzheimer's disease awareness, education, and access to research by sponsoring community engagement programming led by trusted patient advocacy organizations. On these three goals, Biogen will work closely with the NMQF, which has initiated several pioneering projects to increase diversity in clinical trials and is a national leader in using social media to provide trusted health information to communities of color.

Biogen is partnering with the NMQF in its launch of the Alliance for Representative Clinical Trials (ARC). ARC is organized to diversify and bring clinical trials to communities of color and other communities that have been critically underrepresented in clinical trials. To achieve this goal, ARC has two distinct but related programs: 1) the Principal Investigator (PI) Institute that trains community clinicians to be clinical trial PIs; 2) the Clinical Investigative Site Network, which conducts sponsored clinical trials through a network of PI Institute graduates. Through ARC, Biogen will assist in building out the research infrastructure at community sites and support the training of community clinicians to be PIs and researchers who can contribute to its PMR ENVISION study and RWE initiatives such as ICARE AD and the CDRN.

To strengthen its outreach to diverse communities, Biogen is working with NMQF who has a strong community and social media presence with over 90,000 followers on digital platforms (such as Twitter, Facebook, and LinkedIn), an established network of barber shops and beauty salons, 15,000 community-based individual health champions, and access to For Your Health News – a news aggregator service that offers a continuous flow of links to health articles about communities of color organized from 80,000 news sources.

For over two and a half years, Biogen has been partnering with NMQF to build and maintain a web-based data warehouse and geographical information system (referred to as an Index) that houses, aggregates, and analyzes Medicare Fee for Service, Medicare Advantage, and Medicaid claims data on Alzheimer's disease and other neurological conditions. Specific to Alzheimer's disease, users can generate well over 5 million maps, charts, and tables concerning the disease by geography (zip code, county, state, metropolitan statistical areas, and state and congressional legislative districts), by demographic cohort (age, gender, and

race and ethnicity), and by provider (primary and specialty care, hospital, and clinic and pharmacy). The Index is a research platform that uses data visualization to present data in a pictorial or graphical format. It enables decision makers and cross-functional teams to see analytics presented visually, so they can more easily grasp difficult concepts or identify new patterns. The Index will be an important research and publishing platform where findings from the Biogen's PMR ENVISION study and RWE initiatives such as ICARE AD and the CDRN can be analyzed for public consumption and made accessible through data visualization.

In combination with the Index, Biogen and NMQF are partnering to build a Clinical Trial Learning Community (CTLC), designed to be a virtual space where local investigator sites can interact with local providers, community leaders, and industry towards a common objective: reduce disparities in care and outcomes for underrepresented patient populations by ensuring awareness of and access to available clinical trials close to home. Biogen and NMQF invite experts and clinical trial sites will join the CTLC Champions to plan clinical quality improvement and community engagement, with an initial focus on mutual learning about the needs of the local population of patients and caregivers living with Alzheimer's disease.

This initiative aims to develop a blueprint for launching a virtual CTLC in multiple target regions. The CTLC Champions will share local data derived from the Index, notable practices and procedures, and community engagement strategies, and use them to foster changes that facilitate clinical trial participation among underrepresented populations. The CTLC aims to address clinical, social, cultural, and logistical considerations related to clinical trial participation, and increase the options available to underrepresented patient populations living with Alzheimer's disease. These programs are being planned to launch in the second half of 2022, initially in the geography of Washington, D.C., Virginia, and Maryland.

In addition, Biogen is liaising with key health equity experts and health care providers, experienced in working with patients from diverse communities, to form the Alzheimer's Disease Underrepresented Populations (AD-UP) Working Group. The working group provides key insights and solutions to increase the diversity of patients involved in clinical research, as well as educational topics relevant to the underrepresented community.

Biogen has convened a patient advocacy group steering committee with global Alzheimer's disease community leaders since 2018. This group provides ongoing feedback and insights on priority topics, including best practices on engaging with underrepresented communities, and recruitment and enrollment in clinical trials.

The Biogen Medical organization is also leading several Health Equity Initiatives. The overarching mission is to advance critical conversations on key Alzheimer's Disease topics in order to help patients and caregivers by providing education and awareness to all health care providers. Biogen has developed 5 TED Talk like videos covering a wide range of topics focused on

- Underserved and Underrepresented Populations Patient Journey
- Cultural Competence and Cultural Humility
- Role of the Caregiver
- Impact of Comorbidities on Prognosis and Diagnosis
- Successful Engagement for Research/Study Participation

Biogen is partnering with the Balm in Gilead to launch the Faith and Healthy Aging network. This initiative will educate African- Americans on brain health through their faith communities and will start in the first half of 2022.

Additionally, to illustrate the result of the diversity efforts, Biogen's Digital Health Intuition Study (running in partnership with Apple) – which aims to develop a better understanding of the overall brain health of people from all walks of life and backgrounds – has enrolled 11,800 of the 23,000 anticipated participants as of early March 2022. Thirty percent of current enrolees self-identified as non-Caucasian – including 12.6% identifying as Asian, 9.6% identifying as Hispanic, and 9.1% identifying as African American. A detailed description can be found at https://www.intuitionstudy.com/.

Biogen's three-pronged approach to gathering real-world evidence in Alzheimer's disease

As different modalities of data collection vary in the depth of clinical information and the breadth of patient representation, a single data source is unable to RWE in ADprovide a comprehensive understanding of the patient journey across various settings of care with all the outcomes needed to evaluate disease progression and treatment outcomes. Hence, as outlined below, Biogen is committed to partner with established and emerging research stakeholders in the following three multi-modal, real-world research initiatives, which will together provide powerful insights into the Alzheimer's disease patient's journey and the safety, effectiveness, and value of treatments for Alzheimer's disease.

1. ICARE AD: a real-world product-specific registry

In 2021, Biogen launched ICARE AD-US, a product-specific patient registry (NCT05097131) to track long-term cognitive, functional, and behavioral outcomes, identify any serious adverse events, and characterize ARIA frequency and severity in patients on an anti-amyloid monoclonal antibody for the treatment of Alzheimer's disease in a real-world setting.[23] In addition, ICARE AD will provide insight into the health care resource utilization of patients with Alzheimer's disease and the burden placed on informants and care partners.

This study aims to enroll approximately 6,000 patients with early-stage Alzheimer's disease from approximately 200 sites representing diverse settings of care in the United States, from which at least 16% will belong to the African American and Hispanic underrepresented racial and ethnic population. Clinical outcome measures include cognitive, functional, and behavior scales sensitive to change in early-stage Alzheimer's disease. This study will focus on patient-centric clinically meaningful outcomes by capturing several patient-reported outcomes (PROs), including quality of life, care partner burden, and patient and care partner global impression of health over time.

From an evidence generation perspective, there are multiple benefits of ICARE AD-US. For example, seeing prescribing practices in a real-world setting will allow us to understand appropriate use of a treatment, provide perspectives on the patient journey from diagnosis of MCI/mild Alzheimer's disease to administration of treatment, help identify potential roadblocks on the patient journey, help create a more cohesive pathway than is typically seen in fragmented dementia care, and help us understand how patients with Alzheimer's disease are managing multimorbidity. Finally, it is hoped that ICARE AD will be integrated into larger evidence generation initiatives, providing ample opportunities to compare the effectiveness of treatment in broader patient populations. Biogen believes these RWE initiatives will contribute to other initiatives and Biogen stands ready to collaborate with the UsAgainstAlzheimer's ADEA initiative across public and private stakeholders, now in early stages of development, to define and use common standards in protocols and data management that will help in shaping this foundation for future research. ICARE AD may also be embedded into the planned Alzheimer's Association's registry and ALZ-NET and be part of a larger effort to collect meaningful RWE on patients with Alzheimer's disease.

2. Clinical Data Research Network (CDRN): a decentralized prospective observational disease-specific study

Biogen is initiating a 5-plus year decentralized prospective observational CDRN study, which plans to involve over 50,000 patients with Alzheimer's disease who are eligible for treatment with an anti-amyloid monoclonal antibody. Biogen will leverage the scientific consortium, infrastructure, and platforms involved with Biogen's Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS) initiative, to kick start this CDRN for Alzheimer's disease.[24,25] MS PATHS is a global CDRN involving 10 leading MS centers with data on >19,000 MS patients, providing key information on the patient journey and treatment effectiveness and safety, resulting in nearly 150 peer-reviewed manuscripts and scientific presentations. Being disease- rather than product-specific, the CDRN will enable comparative effectiveness and safety research across and between amyloid-directed monoclonal antibodies. This broad disease approach will deepen understanding of the disease mechanism, patient trajectory, and treatment response.

The CDRN study aims to observe the standard of care (SOC) of the patient at the clinic level, with additional data from the patient (e.g., cognition, function, and behavior) and caregivers (e.g., quality of life) collected digitally via an eData Collection platform on an iPad and integrated into the scheduling workflow, and with the data made visible to the treating physician in the same visit. Data will be collected in line with standard clinical practices (i.e., 6-monthly visits, either remotely or in-clinic). The patient will be routinely monitored by MRI; MRI sequences will be standardized to ensure they are comparable across sites. Patients can opt-in to additional blood measures.

The primary network will consist of a nucleus of leading members of the scientific consortium. Additionally, to ensure a diverse population representative of the Medicare population, an additional >100 sites with lighter digital data collection on 45,000 patients will be incorporated. The inclusion of these additional centers will ensure the network reflects the SOC, inclusive of all Alzheimer's disease clinics.

3. Medicare claims analyses: RWE to inform identification, diagnosis, and management of Alzheimer's disease

Medicare claims data are routinely used for a variety of scientifically rigorous research projects with the claims seen as a more reliable source of long-term patient data than private insurance claims, as patients typically remain on Medicare.[26] The data is routinely collected from patients in all geographic regions and all sites; therefore, there is a much larger

population of patients than registries or CDRN. Furthermore, claims data overcome the limitations of single-site sourced data by collecting clinical and resource utilization data (including frequency of MRI monitoring during the titration period, dosing, discontinuation of treatment, outpatient visits, hospitalizations, emergency department visits, and pharmacy utilization), thus providing a unique and powerful tool for gaining insights into the patient journey across all settings of care. Additionally, Medicare enrollees are racially and geographically diverse and a claims-based study offers a diverse pool of patients; in 2019, 10.4% of Medicare beneficiaries were Black, 9% were Hispanic, and 4.2% were Asian/Native Hawaiian and Pacific Islander.[27]

The Medicare dataset is particularly useful for gaining insights around safety and the appropriate use of amyloid-directed monoclonal antibodies. Biogen has launched the development of a claims-based algorithm for detecting ARIA using a series of clinical and procedural codes, which will facilitate the identification of the most serious adverse events at scale. Furthermore, by providing patient-level resource utilization and cost data, utilization of this dataset will assist with filling in the gaps regarding costs of MCI and costs of comorbidities, which are not currently captured in the literature.

As mentioned above, through close collaboration with NMQF and ARC, Biogen will assist in building out the research infrastructure at community sites and support the training of community clinicians to be PIs and researchers who can contribute to its Post Marketing Requirement (PMR) ENVISION Study and RWE initiatives such as ICARE AD, the CDRN and other efforts.

Conclusion

While RCTs remain the gold standard for efficacy because they deliver the highest level of evidence given the scientific rigor and robust methodology, evidence from a real-world setting plays a critical role in extrapolating and augmenting RCT for efficacy data to build a bigger and clearer picture of a drug's utilization, safety, effectiveness, and value in everyday clinical practice. As part of the evidence continuum, RWE offers important information about the effectiveness and safety of a drug in larger and more heterogeneous populations and its value is well founded across multiple therapy areas. Building upon the experience in generating large-scale RWE – most recently in MS and SMA[18,24] – Biogen is committed to generating rigorous RWE to further characterize the value of FDA-approved Alzheimer's treatments to the field through a comprehensive three-pronged data generation approach.

Our emphasis on RWE is consistent with calls for leadership and coordinated action in accordance with principles outlined in 2016 by senior officials from FDA, CMS, NIH, AHRQ, Department of Veterans Affairs and other health agencies. All these data generation efforts are intrinsically adaptable to address the questions and needs of the new treatment environment for Alzheimer's disease and all these efforts will ultimately help develop the treatment and research ecosystem to advance the much-needed care of patients with Alzheimer's Disease.

Biogen is confident that comprehensive data generation efforts, through the confirmatory PMR study, ENVISION, and all the proposed RWE efforts in partnership with organizations like NMQF and others will conclusively address any remaining questions that CMS and the broader community have about the effectiveness and safety of anti-amyloid monoclonal antibodies in a broad patient population, including the underserved communities. For all the approaches outlined above, Biogen is committed to sharing both the data and analysis thereof with the relevant agencies, including CMS, FDA, and NIH, on an ongoing and regular basis.

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Conflicts of interest:

MR, MLB, KH, and CM are employees and shareholders of Biogen.

GP, GW, and MM are employees of the National Minority Quality Forum, which has received funding from Biogen.

References

1. Stanley K. Design of randomized controlled trials. Circulation 2007;115:1164–1169.

2. Hariton E, Locascio JJ. Randomised controlled trials – the gold standard for effectiveness research. BJOG Int J Obstet Gynaecol 2018;125:1716–1716.

3. U.S. Food and Drug Administration. Accelerated approval pathway. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval (Accessed March 17, 2022).

4. PhRMA. Accelerated Approval: Bringing Patients Access to Needed Medicines. https://phrma.org/resource-center/Topics/Access-to-Medicines/Accelerated-approval-Bringing-patients-access-to-needed-medicines (Accessed March 17, 2022).

5. Friends of Cancer Research. Regulatory Focus – Pazdur mounts defense of accelerated approval during Cures 2.0 panel. https://friendsofcancerresearch.org/news/regulatory-focus-pazdur-mounts-defense-of-accelerated-approval-during-cures-2-0-panel/ (Accessed March 17, 2022).

6. National Cancer Institute. Cancer Stat Facts: Myeloma. https://seer.cancer.gov/statfacts/html/mulmy.html (Accessed March 17, 2022).

7. U.S. Food and Drug Administration. Considerations for the use of real-world data and real-world evidence to support regulatory decision-making for drug and biological products. 2021. Available from: https://www.fda.gov/media/154714/download (Accessed March 17, 2022).

8. Bolislis WR, Fay M, Kühler TC. Use of Real-world Data for New Drug Applications and Line Extensions. Clin Ther 2020;42:926–938.

9. U.S. Food and Drug Administration. Framework for FDA's real-world evidence program. 2018. Available from: https://www.fda.gov/media/120060/download (Accessed March 8, 2022).

10. Bonamici S. H.R.34 - 114th Congress (2015-2016): 21st Century Cures Act. 2016. Available from: https://www.congress.gov/bill/114th-congress/house-bill/34/ (Accessed March 3, 2022).

11. US Food and Drug Administration. 21st Century Cures Act. https://www.fda.gov/regulatoryinformation/lawsenforcedbyfda/significantamendmentstothefdcact/21stcenturycuresact/default.htm (Accessed March 3, 2022).

12. DeGette D. H.R.6000 - 117th Congress (2021-2022): Cures 2.0 Act. 2021. Available from: https://www.congress.gov/bill/117th-congress/house-bill/6000?q=%7B%22search%22%3A%5B%22cures+2.0%22%2C%22cures%22%2C%222.0%22%5D%7D&s=1&r=1 (Accessed March 8, 2022).

13. Association of American Medical Colleges. Reps. DeGette and Upton Introduce Cures 2.0 Act, Including ARPA-H Authorization. 2022. Available from: https://www.aamc.org/advocacy-policy/washington-highlights/reps-degette-and-upton-introduce-cures-20-act-including-arpa-h-authorization (Accessed 4 March 2022).

14. Centers for Disease Control and Prevention. Largest CDC COVID-19 vaccine effectiveness study in health workers shows mRNA vaccines 94% effective. 2021. Available from: https://www.cdc.gov/media/releases/2021/p0514-covid-19-vaccine-effectiveness.html (Accessed March 14, 2022).

15. Cystic Fibrosis Foundation. Patient Registry. 2022. Available from: https://www.cff.org/medical-professionals/patient-registry (Accessed March 14, 2022).

16. Rothwell PM. Factors That Can Affect the External Validity of Randomised Controlled Trials. PLoS Clin Trials 2006;1:e9.

17. Sledge GW, Hudis CA, Swain SM, et al. ASCO's approach to a learning health care system in oncology. J Oncol Pract 2013;9:145–148.

18. Hagenacker T, Wurster CD, Günther R, et al. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study. Lancet Neurol 2020;19:317–325.

19. European Medicines Agency. Spinraza: summary of product characteristics. 2018. Available from: https://www.ema.europa.eu/en/documents/product-information/spinraza-epar-product-information_en.pdf (Accessed March 14, 2022).

20. Centers for Medicare & Medicaid Services. Monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease. 2022. Available from: https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&NCAId=305 (Accessed March 17, 2022)

21. UsAgainstAlzheimer's. UsAgainstAlzheimer's Urges CMS to Revise Plan that would Deny Medicare Coverage of FDA-approved Alzheimer's Drugs. 2022. Available from: https://www.usagainstalzheimers.org/press/usagainstalzheimers-urges-cms-revise-plan-would-deny-medicare-coverage-fda-approved (Accessed March 8, 2022).

22. Alzheimer's Association. Alzheimer's Association announces national effort to collect "real world" data on newly-approved treatments. 2021. Available from:

https://alz.org/news/2021/alzheimers-association-announces-national-effort (Accessed March 8, 2022).

23. Galvin JE, Cummings JL, Levitchi Benea M, et al. ICARE AD-US: design of a prospective, single-arm, multicenter, noninterventional real-world study of aducanumab in the United States. Alzheimer's Association International Conference 2021, Denver, CO, USA.

24. Mowry EM, Bermel RA, Williams JR, et al. Harnessing Real-World Data to Inform Decision-Making: Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS). Front Neurol 2020;11:632.

25. Multiple Sclerosis Partners Advancing Technology and Health Solutions. MS PATHS. 2022. Available from: https://www.mspaths.com (Accessed March 14, 2022).

26. Mues KE, Liede A, Liu J, et al. Use of the Medicare database in epidemiologic and health services research: a valuable source of real-world evidence on the older and disabled populations in the US. Clin Epidemiol 2017;9:267–277.

27. Yang J. Distribution of Medicare beneficiaries in 2019, by ethnicity. 2021. Available from: https://www.statista.com/statistics/248039/distribution-of-medicare-beneficiaries-by-ethnicity/ (Accessed March 14, 2022).