Siponimod for Secondary Progressive Multiple Sclerosis & Esketamine for Treatment-Resistant Depression

Public Meeting – May 23, 2019

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Siponimod for Secondary Progressive Multiple Sclerosis: Effectiveness and Value

Morning Session – May 23, 2019

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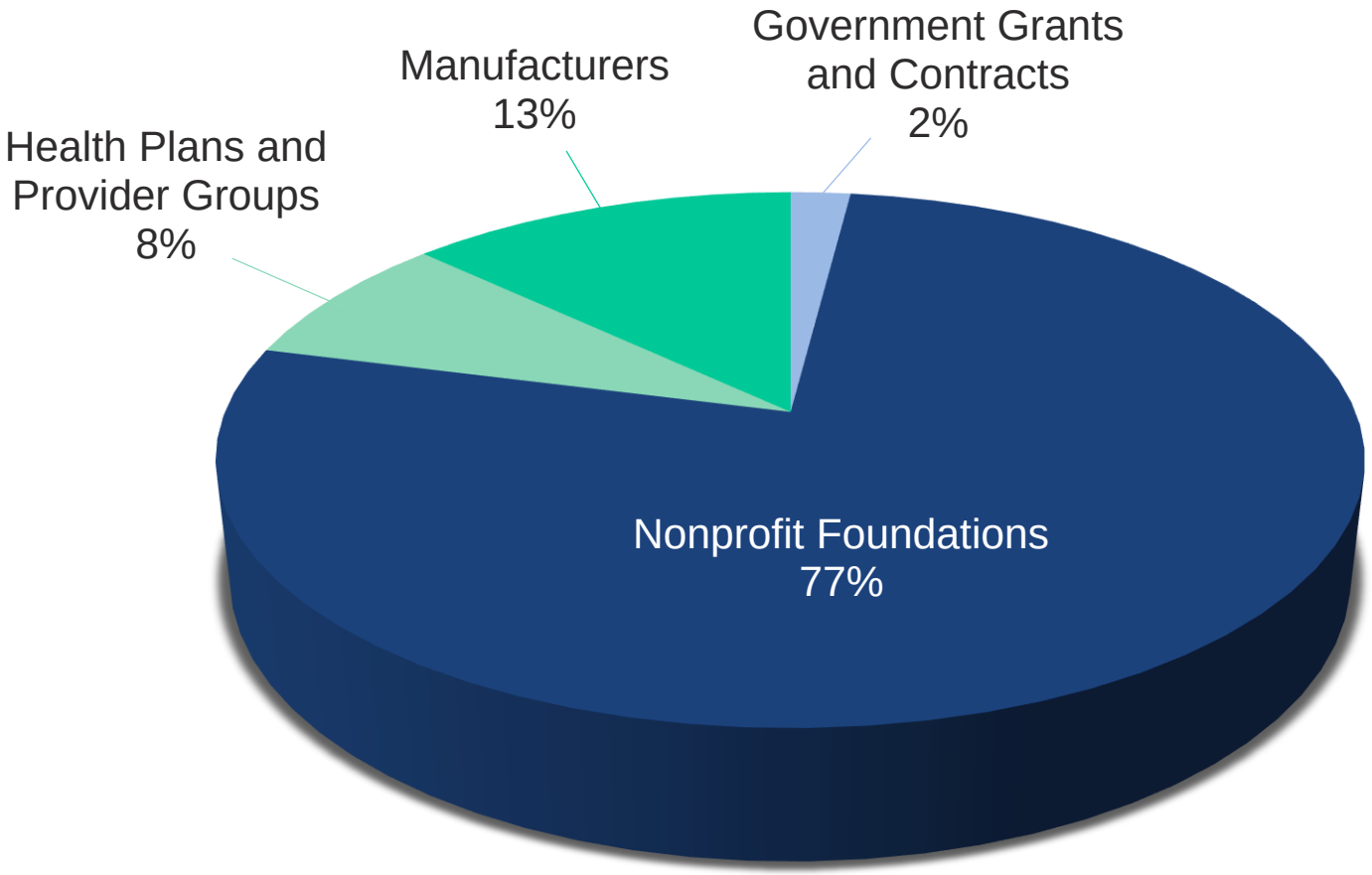
Organizational Overview

- Midwest Comparative Effectiveness Public Advisory Council (CEPAC)

- The Institute for Clinical and Economic Review (ICER)

2019 Funding Sources



ICER Policy Summit and non-report activities

Why are we here today?

- *"As my MS specialist said, I have now moved out of the heavily funded relapsing remitting research category to the little known, least explored category of SPMS.... I may have a rough road ahead."*

  – Patient Comment on MS Coalition Patient Survey

- *"[Siponimod is] an important approval and will hopefully stimulate important research... Price is an important factor in determining access to a medication. So while Mayzent is not priced at the top of the MS drug list, we believe the price is still too high."*

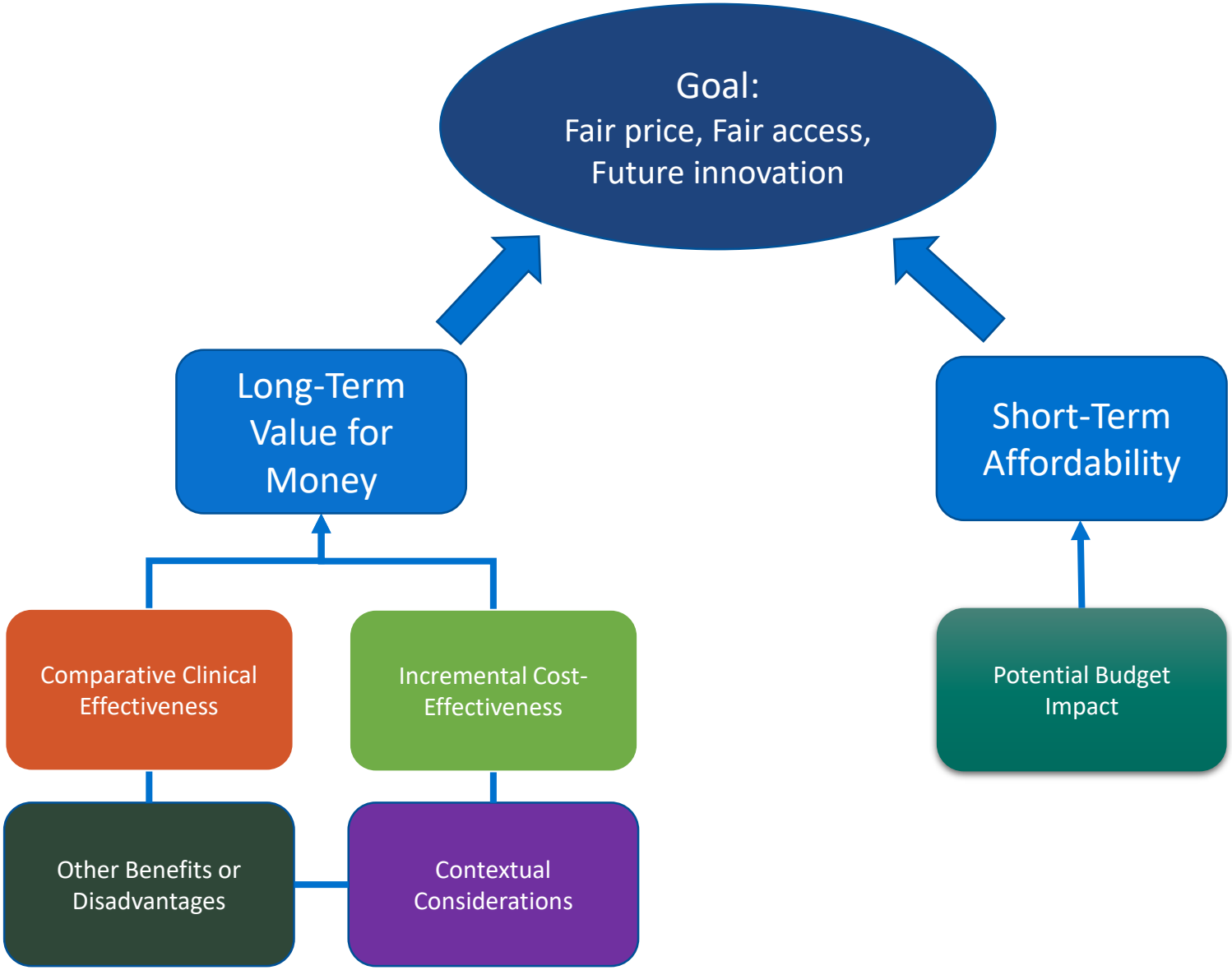
  -Kathleen Costello, Associate Vice President of Healthcare Access, National MS Society

Why are we here today?

- Unmet need for patients with a serious, progressive illness
- New drugs in these areas often raise questions about appropriate use, cost
- Employers struggling to maintain affordable health benefits
- Patients can have difficulty accessing drugs
- Benefit of objective evaluation and public discussion of the evidence on effectiveness and value

How was the ICER report developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- ICER evidence analysis
- University of Washington cost-effectiveness modeling team
- Public comment and revision
- Expert reviewers
  - Three neurologists
  - Two patient groups
- How is the evidence report structured to support CEPAC voting and policy discussion?


Goal:
Fair price, Fair access,
Future innovation
Long-Term Value for Money
Short-Term Affordability
Comparative Clinical Effectiveness
Incremental Cost-Effectiveness
Potential Budget Impact
Other Benefits or Disadvantages
Contextual Considerations

Agenda

Morning Session: Siponimod for Secondary Progressive Multiple Sclerosis	
9:00 am—9:15 am	Meeting Convened and Opening Remarks Steve Pearson, MD, MSc, President, ICER
9:15 am—10:15 am	Presentation of the Evidence • Ravi Sharaf, MD, MS, Associate Professor of Medicine, Weill Cornell Medicine • Lisa Bloudek, PharmD, MS, CHOICE Institute, Department of Pharmacy, University of Washington
10:15 am—10:30 am	Manufacturer Comments and Discussion
10:30 am—10:50 am	Public Comments and Discussion
10:50 am – 11:00 am	Break
11:00 am – 11:40 am	Midwest CEPAC Panel Vote on Clinical Effectiveness and Value
11:40 am—12:15 pm	Key Policy Discussion
12:15 pm – 1:00 pm	Lunch

Clinical and Patient Experts

Bruce A. Cohen, MD, Professor, Davee Department of Neurology and Clinical Neurological Sciences, Northwestern University Feinberg School of Medicine

- *Dr. Cohen receives consulting income from Biogen, Celgene, EMD Serono, receives research funding through Northwestern University from Hoffman La Roche/Genentech and MedDay, and owns stock in Abbott Laboratories, AbbVie, and CVS Health.*

Annette M. Langer-Gould, MD, PhD, Lead for Clinical and Translational Neuroscience, Southern California Permanente Medical Group/Kaiser Permanente

- *No relevant conflicts of interest to disclose*

Hollie Schmidt, VP of Scientific Operations, Accelerated Cure Project for Multiple Sclerosis

- *No relevant conflicts of interest to disclose.*

Ann Moore, *SPMS Patient*

- *No relevant conflicts of interest to disclose.*

Evidence Review

Ravi N. Sharaf MD, MS

Associate Professor of Medicine

Weill Cornell Medicine

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Key Collaborators

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  Director, Evidence Review, ICER
- **Noemi Fluetsch, MPH**

  Research Assistant, ICER
- **Serina Herron-Smith, BA**

  Research Assistant, ICER

Disclosures:

We have no conflicts of interest relevant to this report.

Background

Scope of Review

- This project assesses the comparative clinical effectiveness and economic impact of siponimod in the treatment of secondary progressive multiple sclerosis (SPMS)

Multiple Sclerosis (MS) Background

- A chronic, inflammatory, demyelinating, and neurodegenerative disease of the central nervous system (CNS)
- Up to 1 million affected in the US
- Disease-related costs (~ $24 billion/year) in the US are estimated to rise as prescription prices outpace inflation

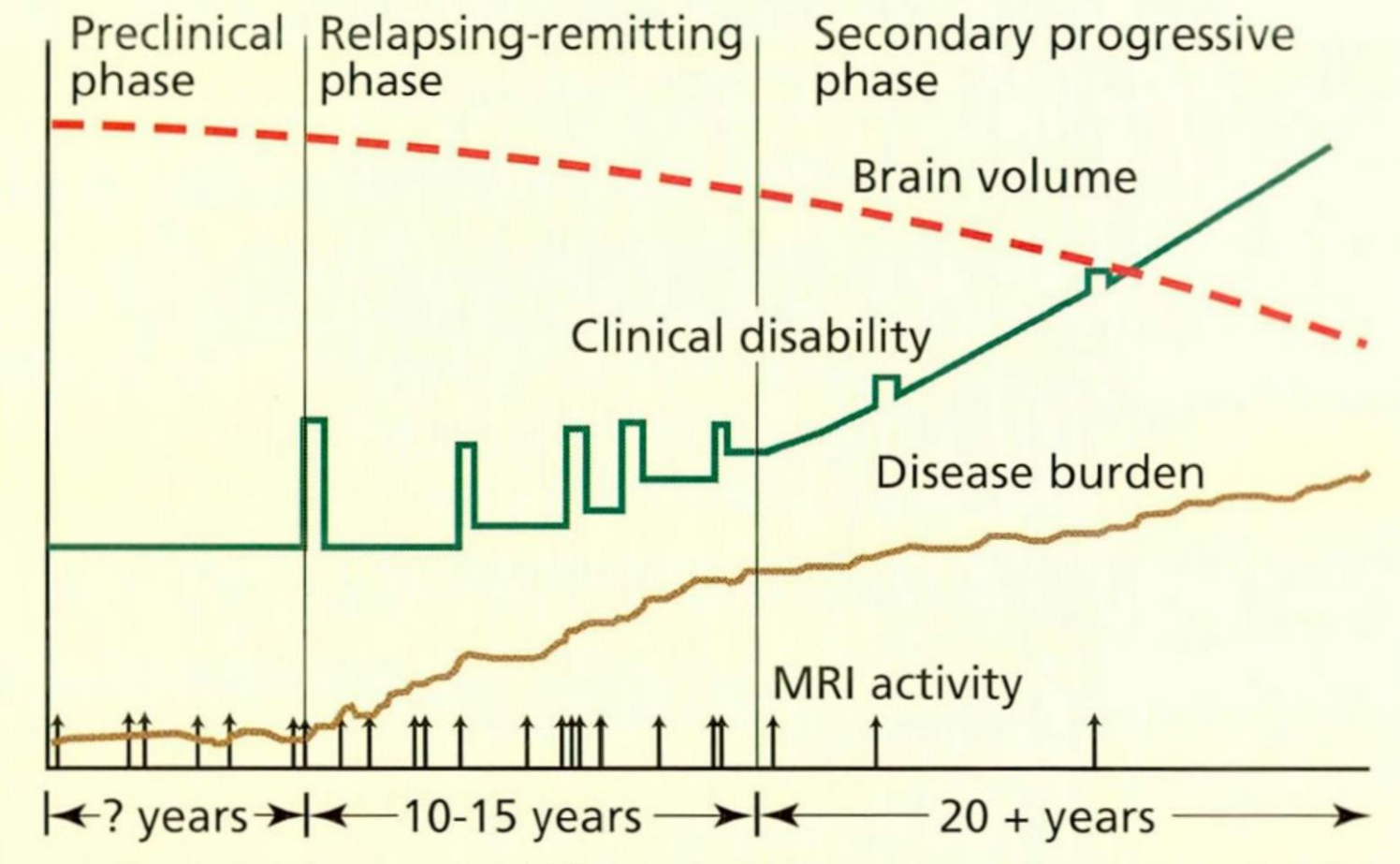
MS Nomenclature: Relapsing Remitting MS (RRMS)

- Initial presentation of 85% to 90% of MS patients
- Relapses: *Episodic* development of neurologic symptoms that may resolve
  - Incomplete symptom resolution→ disability progression
  - Relapses usually reflect MRI-detectable CNS inflammation or lesions

MS Nomenclature: Progressive MS

- Characterized by increasing neurologic disability progression that occurs independent of, or in the absence of, relapse (unlike RRMS)
- Active or Not Active
  - Active =presence of clinical relapse or MRI findings consistent with MS
- Primary Progressive MS (PPMS)
  - Progressive course from disease onset
- Secondary Progressive MS (SPMS)
  - Progressive course after RRMS

RRMS/SPMS Clinical Course



Fox RJ, Cohen JA: Multiple sclerosis: the importance of early recognition and treatment. *Cleve Clin J of Med,* 2001; 68:157–70.

Impact on SPMS Patients- MS Coalition Survey

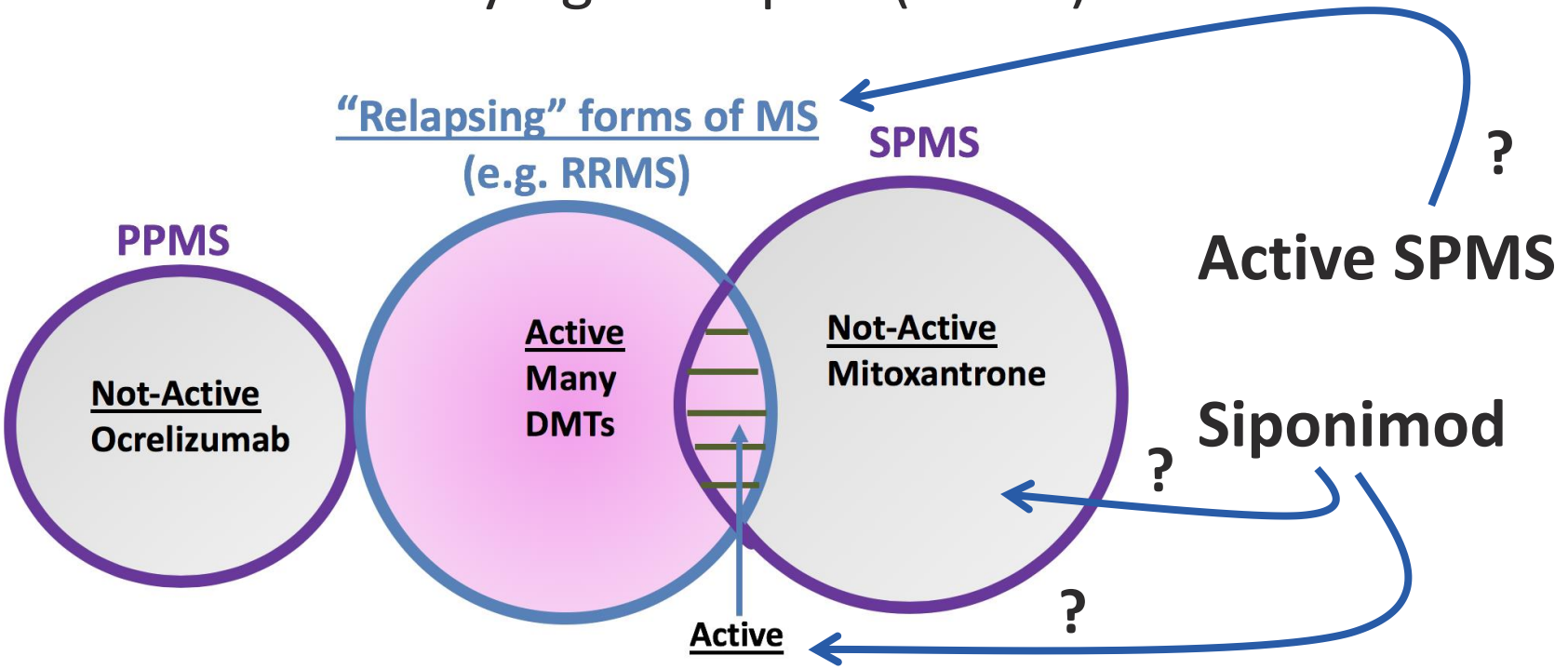
"I lost the ability to stand, transfer, or walk a few steps (with a walker) in 2010, which had a huge impact on my life. My cognitive function has continued to become more impaired."

"I thought I would be working outside the home by now, but my options are really limited. Because of this, our finances are tighter than I thought they'd be. My kids know that I can't do what a lot of other moms can do. My husband has to do so much more because of it."

"I've given up thinking that there is anything out there to help me."

Treatment Options for SPMS

- Therapeutic goal in MS is to decrease disease activity and disability progression
- Disease modifying therapies (DMTs)

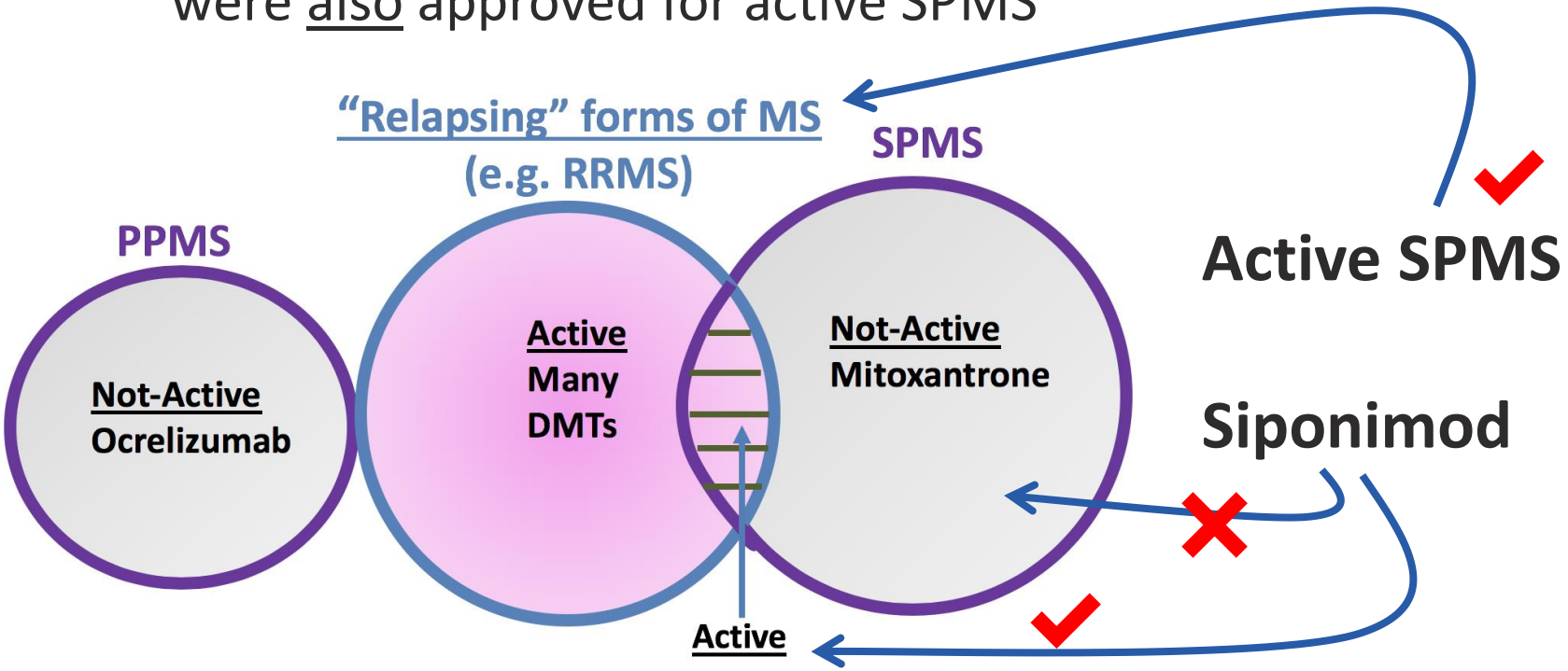


Siponimod (Mayzent™, Novartis)

- Novartis application for siponimod label for active and non-active SPMS
- Oral selective sphingosine-1-phosphate (S1P) receptor modulator
  - Anti-inflammatory activity
- Mechanism of action similar but not identical to fingolimod (FDA approved for relapsing MS)

FDA Review of Siponimod (March 2019)

- Siponimod approved only for relapsing forms of MS, now explicitly noted to include "active SPMS"
  - FDA clarified that DMTs approved for relapsing forms of MS were also approved for active SPMS



Methods in Brief

Methods: Evidence Review

- Systematic Review following PRISMA guidelines
- Comparators
  - Treatments with some efficacy in SPMS or are commonly used in practice (regardless of FDA indication)
    - Best supportive care
    - Ocrelizumab
    - Beta interferons
    - Natalizumab

Outcomes

- Progression
  - Expanded Disability Status Scale (EDSS)

  - Confirmed Disability Progression at 3 months (CDP-3)
    - 1-point increase in EDSS score (or 0.5-point increase if the patient's baseline EDSS ≥ 5.5) confirmed 3 months
  - Timed 25 Foot Walk Test
- Relapse
  - Clinical relapse
  - MRI evidence of new lesions

Results

Literature Search Results

- One Phase 3 trial (EXPAND) identified of siponimod in patients with SPMS
- No head-to-head studies of siponimod versus an active comparator
- Two studies of ocrelizumab (PPMS, Relapsing MS)
- Unable to perform network meta analysis
    - Differences in study eligibility criteria, enrolled patient demographics, study endpoints
- Matching-adjusted indirect comparison

Siponimod: EXPAND Trial

- Patients with SPMS (n = 1600) randomized 2:1 to siponimod vs. placebo
- FDA Review
  - Methodologic Concerns
    - Possible compromised blinding
  - Misclassification (late RRMS vs SPMS?)

Siponimod: EXPAND Trial Results

- Decreased relapses in overall SPMS population
- Decreased progression
  - CDP-3: 26% (siponimod) vs 32% (placebo)
    - HR 0.79; (95% CI 0.65, 0.95), NNT ~19
  - Active disease: HR ~0.65
  - Non-active disease: HR ~0.85 (upper bound CI ~1.05)
- Worsening in timed 25-foot walk test: 40% vs 41%

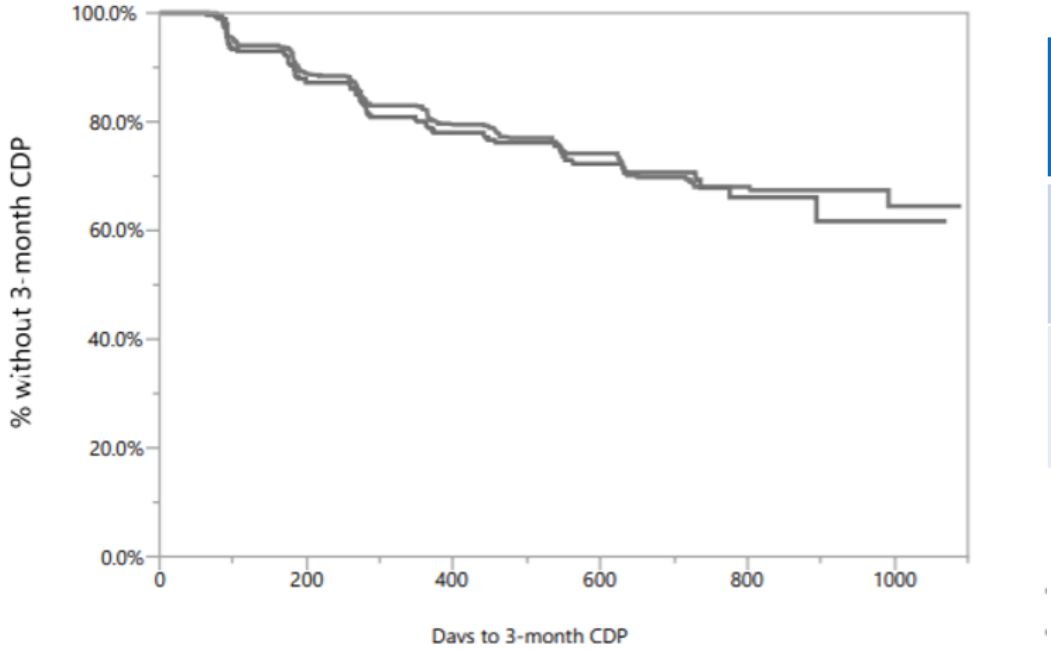
Progression Independent of Relapse Activity

- Relapses a potential confounder of CDP results.
- EXPAND investigator-initiated post-hoc analyses
  1. Principal stratum analysis (patients predicted not to relapse regardless of treatment assignment)
  2. Hypothetical strategy
     a) Censoring at Relapses
     b) Simulate same relapse rate in both treatment arms
- Estimated CDP-3 hazard ratio ranged from 0.80-0.86*

*Cree et al 2018 Poster Presentation S8.005 (April 22, 2018)

FDA Post-Hoc Analysis: EXPAND Trial CDP-3

- Patients with NO relapses before (2 years) or during study



	CDP-3
Siponimod	25.5%
Placebo	26%

- "The pivotal trial results provide insufficient evidence to support a claim that siponimod is effective in patients with SPMS who are not continuing to have relapses, i.e., in patients with non-active SPMS"

Center for drug evaluation and research, *Application number:* 209884orig1s000, FDA summary review

Harms: Siponimod

- Most adverse events were not medically serious, and were treatable, or reversible
- Treatment discontinuation
  - Siponimod (8.2% of patients): Bradyarrythmia
  - Placebo (4.9% of patients): Fatigue

Ocrelizumab (PPMS, RMS): ↓Disability (CDP-3)

Study	Ocrelizumab	Placebo	Hazard Ratio
PPMS ORATORIO	33%	39%	0.76 (0.59-0.98)
	Ocrelizumab	**IFN Beta-1a**	**Hazard Ratio**
Relapsing MS OPERA I & II	9%	14%	0.60 (0.45-0.81)

Controversies and Uncertainties (1)

- Lack of comparative effectiveness data in SPMS
- Discrepancy between outcomes (CDP-3/Walk test)
- FDA Input:
  - Does siponimod work in non-active SPMS (i.e. independent of its effect on relapse)?
    - FDA: “insufficient evidence”
    - EXPAND investigators: post-hoc analyses “confirm an effect”

*Cree et al 2018 Poster Presentation S8.005 (April 22, 2018)

Controversies and Uncertainties (2)

- FDA Input (continued)
  - Drop out after relapse in placebo arm (8%) vs siponimod (3%)
  - Prior FDA concerns mentioned

Potential Other Benefits and Contextual Considerations

- SPMS has high lifetime burden of illness
- Few medications with data to support use in SPMS
- A delay in disease progression and activity may improve patient-centered outcomes and caregiver burden
- Siponimod is an oral therapy

Public Comments Received

- ICER should discontinue review after the FDA label came out

Summary

- SPMS is a devastating disease that impacts patients and their caregivers
- Siponimod reduces relapses and has manageable harms in active SPMS
- Uncertainty regarding siponimod's benefit on progression independent of relapses (non-active SPMS)

ICER Evidence Ratings for Siponimod

- We have high certainty that siponimod provides at least a small net health benefit in patients with active SPMS compared to best supportive care ("B+")
- We have low certainty about the net health benefit of siponimod versus best supportive care in patients with non-active SPMS ("I")*
- We have insufficient data to conclude that the net health benefit of siponimod is superior/inferior to any of other medication used in SPMS ("I")

*informed by FDA data, and a change from most recent ICER report

Questions?

Cost-Effectiveness

Lisa Bloudek, PharmD, MS

The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute, Department of Pharmacy

University of Washington

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Key Review Team Members

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Disclosures:

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University of Washington researchers have no conflicts to disclose defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care manufacturers or insurers.

Objective

Estimate the cost-effectiveness of siponimod for the treatment of SPMS in 1) the overall SPMS population and 2) the subpopulation with active SPMS*

*Evidence of relapses within two years of enrollment as a proxy for active SPMS

Methods in Brief

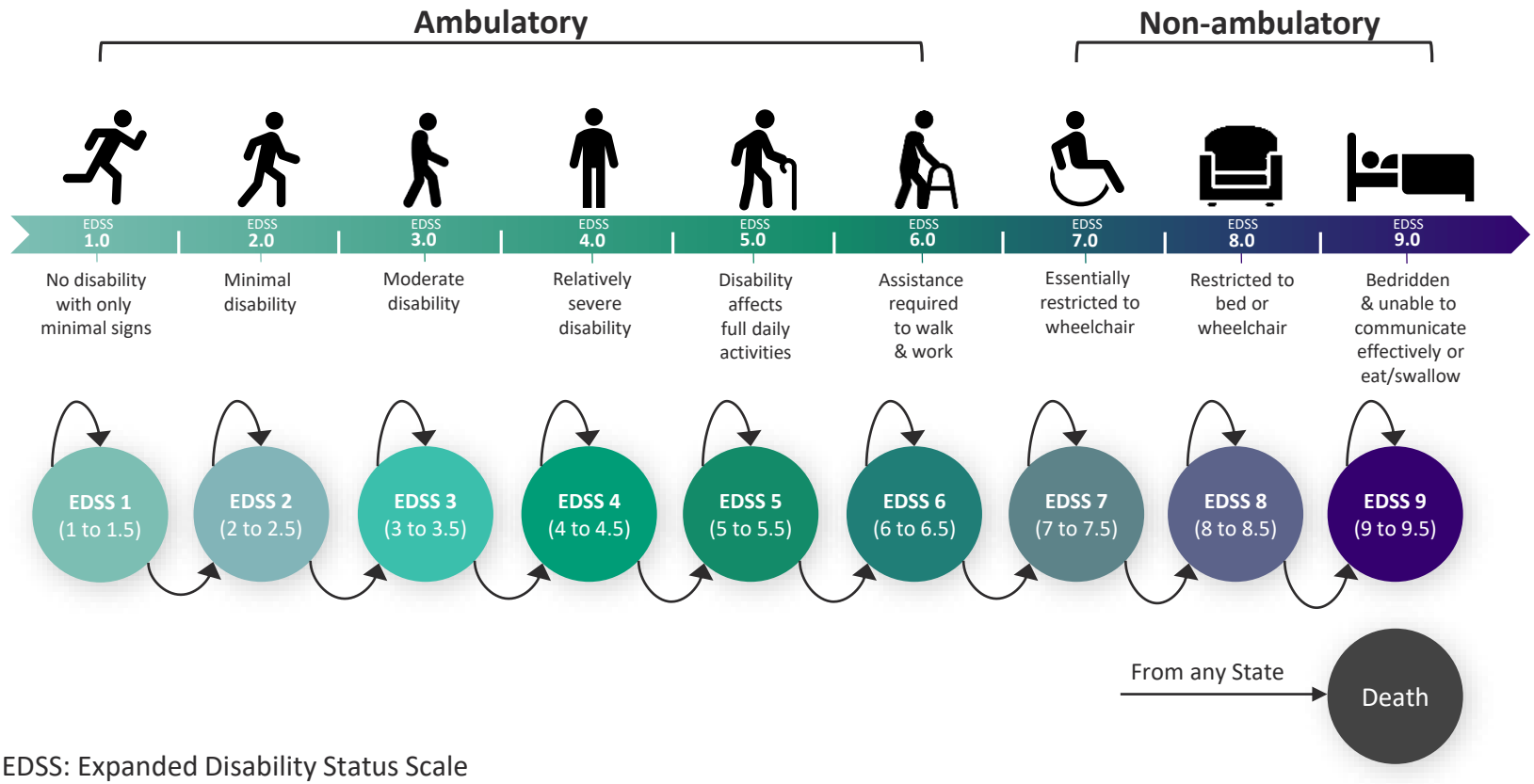
Methods Overview: Base Case

- **Model**: Markov Model
- **Setting**: United States
- **Perspective**: Health Care Sector Perspective
- **Time Horizon**: Lifetime
- **Discount Rate**: 3% per year (costs and outcomes)
- **Cycle Length**: 1 Year
- **Primary Outcomes**: Cost per LY gained; cost per LY of ambulation gained; cost per QALY gained

BSC: best supportive care, LY: life-years, QALYs: quality-adjusted life years

Model Schematic

- Health states based on EDSS



EDSS: Expanded Disability Status Scale

Model Characteristics

- Each EDSS health state is associated with a risk of relapse, utility, risk of mortality, and direct costs
- Natural history transitions between EDSS states based on data from the London-Ontario cohort[1,2]
  - After discontinuation, the patient transitions according to the natural history of SPMS
- Stopping rules:
  - No stopping rule for the overall SPMS population
  - Stopping rule at EDSS 7 for active SPMS

1. Mauskopf J. *J Med Econ.* 2016;19(4):432–42.
2. Scalfari A. *Brain.* 2010;133(Pt 7):1914-1929.

EDSS: Expanded Disability Status Scale, SPMS: secondary progressive multiple sclerosis

Key Model Assumptions

- Base case comparator is best supportive care (BSC)
  - Informed by the placebo arm of the EXPAND trial
  - DMTs are only recommended for patients with active disease
    - No DMTs have consistently demonstrated an impact on progression in SPMS
    - Insufficient evidence to compare siponimod to other DMTs
- Siponimod vs. alternative DMTs explored as a scenario analysis
  - Based on a manufacturer-submitted matching-adjusted indirect comparison (MAIC)

DMT: disease-modifying treatments, EDSS: Expanded Disability Status Scale

Key Model Inputs: Treatment Efficacy

- Treatment efficacy vs BSC from the EXPAND trial[1]
  - HR for disability progression (moving to higher EDSS states)
  - Relative risk of relapse
- 9.4% of patients discontinue siponimod in years 1 & 2[2]
  - 3% per year thereafter (assumption)

	HR for Disability Progression (CI)	RR for Relapse (CI)
Overall SPMS	0.79 (0.65 to 0.95)	0.45 (0.34 to 0.59)
Active SPMS	0.67 (0.49 to 0.91)	0.45 (0.34 to 0.59)

1. Kappos L. *Lancet.* 2018;391(10127):1263-1273.
2. Novartis Manufacturer Data Submission

BSC: best supportive care, CI: confidence interval, EDSS: Expanded Disability Status Scale, HR: hazard ratio, RR: risk ratio, SPMS: secondary progressive multiple sclerosis

Key Model Inputs: Relapses

- Mean number of relapses in the year before screening was 0.2 in the siponimod arm and 0.3 in the placebo arm in the EXPAND trial[1]
- Model assumes 70.8% mild/moderate and 29.2% severe[2,3]

	Annual Relapse Rate (Overall SPMS)		Annual Relapse Rate (Active SPMS)	
EDSS State	Base Case[4]	Range for One-Way SA	Base Case[4,5]	Range for One-Way SA
1	0.00	0.00–0.00	0.00	0.00–0.00
2	0.47	0.42–0.52	0.91	0.82–1.00
3	0.88	0.79–0.97	1.64	1.48–1.80
4	0.55	0.50–0.61	1.05	0.95–1.16
5	0.52	0.47–0.57	1.27	1.14–1.40
6	0.45	0.41–0.50	1.10	0.99–1.21
7	0.34	0.31–0.37	0.82	0.74–0.90
8	0.34	0.31–0.37	0.82	0.74–0.90
9	0.34	0.31–0.37	0.82	0.74–0.90

1. Kappos L. *Lancet.* 2018;391(10127):1263-1273.
2. Nickerson M. *Mult Scler Relat Disord.* 2015;4(3):234-40
3. Zimmermann M. *CNS Drugs.* 2018;32(12):1145-1157.
3. Mauskopf J. *J Med Econ.* 2016;19(4):432–42.
4. Bozkaya D, *J Med Econ.* 2017;20(3):297–302..

EDSS: Expanded Disability Status Scale, SA: sensitivity analysis, SPMS: secondary progressive multiple sclerosis

Key Model Inputs: Utilities

- Utility based on EDSS derived from longitudinal prospective, cohort study of people with MS in the UK
- Additional annualized disutility of 0.091 per mild/moderate relapse and 0.302 per severe relapse[1,2]

EDSS State	Base Case Utility[3]	Range for One-Way SA
1	0.762 ± 0.220*	0.761–0.931
2	0.711 ± 0.221*	0.686–0.838
3	0.608 ± 0.281*	0.640–0.782
4	0.609 ± 0.256*	0.547–0.669
5	0.531 ± 0.286*	0.548–0.670
6	0.481 ± 0.269	0.433–0.529
7	0.397 ± 0.317	0.357–0.437
8	0.021 ± 0.387	0.019–0.023
9	0	0

*Value for all MS diagnoses (not specific to SPMS).

1. Oleen-Burkey M. *Patient.* 2012;5(1):57-69.
2. Zimmermann M. *CNS Drugs.* 2018;32(12):1145-1157.
3. Hawton A. *Value Health.* 2016;19(4):460-8.

EDSS: Expanded Disability Status Scale, MS: multiple sclerosis, SA: sensitivity analysis, UK: United Kingdom

Key Model Inputs: Mortality

EDSS State	Base Case Mortality Multiplier[1]	Range for One-Way SA
1	1.43	1.29–1.57
2	1.60	1.44–1.76
3	1.64	1.48–1.80
4	1.67	1.50–1.84
5	1.84	1.66–2.02
6	2.27	2.04–2.50
7	3.10	2.79–3.41
8	4.45	4.01–4.90
9	6.45	5.81–7.10

1. Pokorski RJ. *J Insur Med.* 1997;29(2):101-106.

EDSS: Expanded Disability Status Scale, SA: sensitivity analysis

Key Model Inputs: Treatment Cost

Drug Name, Labeled Dose, Administration Route	Strength	WAC	Net Price	Acquisition Cost/Year
Siponimod, 1 mg po QD	0.25 mg	$1,697.26 per 28	N/A	$88,561
Siponimod, 2 mg po QD	2 mg	$7,273.97 per 30	N/A	$88,561

- All patients initiating siponimod require genetic screening to identify CYP2C9 metabolic function
- 30% of patients are assumed to require cardiac monitoring for the first dose of siponimod
  - 2 electrocardiograms
  - 1 specialist visit

QD: once daily, N/A: not available, po: oral, WAC: wholesale acquisition cost

Key Model Inputs: MS-Related Costs

- Direct costs include includes non-drug costs (inpatient, outpatient, office visits, medical devices, alterations the house)
- Indirect costs include short term absence, reduced working time/income, and early retirement due to multiple sclerosis

EDSS State	Direct Costs[1]	Range for One-Way SA	Indirect Costs[1] (Scenario Analysis)
1	$5,123	$4,611–$5,635	$15,460
2	$7,266	$6,539–$7,993	$19,619
3	$9,408	$8,467–$10,349	$23,778
4	$11,551	$10,396–$12,706	$27,938
5	$13,694	$12,325–$15,063	$32,097
6	$15,836	$14,252–$17,420	$36,256
7	$17,979	$16,181–$19,777	$40,415
8	$20,121	$18,109–$22,133	$44,575
9	$22,264	$20,038–$24,490	$48,734
Relapse	$3,064[1,2]	$2,758–$3,370	$2,702[1,2]

1. Kobelt G. *Neurology.* 2006;66(11):1696-702.
2. Zimmermann M. *CNS Drugs.* 2018;32(12):1145-1157.
3. Oleen-Burkey M. *Patient.* 2012;5(1):57-69. Inflated to 2018 USD using the medical care component of the Bureau of Labor Statistics Consumer Price Index.

EDSS: Expanded Disability Status Scale, MS: multiple sclerosis, SA: sensitivity analysis

Scenario Analyses

- Key scenarios:
  - Modified societal perspective including indirect costs
  - MAIC analysis of siponimod vs interferon beta-1b
- Additional scenarios:
  - Inclusion of caregiver burden[1]
  - Discontinuation of siponimod at EDSS 8 or 9 in active SPMS
  - Efficacy based on 6-month timepoint of the EXPAND trial
  - Utility values based on Orme 2007[2]
  - Mortality multipliers from Harding 2018[3]
  - Subpopulation with non-active SPMS

1. Acaster S. *BMC Health Serv Res.* 2013;13:346
2. Orme M. *Value Health.* 2007;10(1):54-60.
3. Harding K. *Mult Scler Relat Disord.* 2018;25:186-191.

EDSS: Expanded Disability Status Scale, MAIC: matching-adjusted indirect comparison

Key Scenario: Matching-Adjusted Indirect Comparison (MAIC)

- The manufacturer of siponimod submitted an MAIC comparing siponimod to other DMTs[1]
  - Seeks to provide comparative evidence when traditional evidence synthesis methods are not considered possible or valid
  - Matches patient-level data from EXPAND with aggregate data from individual trials of comparators then adjusts for potential effect modifiers
- Not included as base case due to limitations inherent to MAIC and limitations of the individual comparator trials
  - Inconsistency in endpoints, clinically relevant dosing, ability to fully adjust
- Conducted a scenario of siponimod compared to interferon beta-1b
  - European study of interferon beta-1b most similar to the indicated population with active disease, and relatively few limitations

1. Academic in confidence.

DMT: disease-modifying treatments, MAIC: matching-adjusted indirect comparison

Results

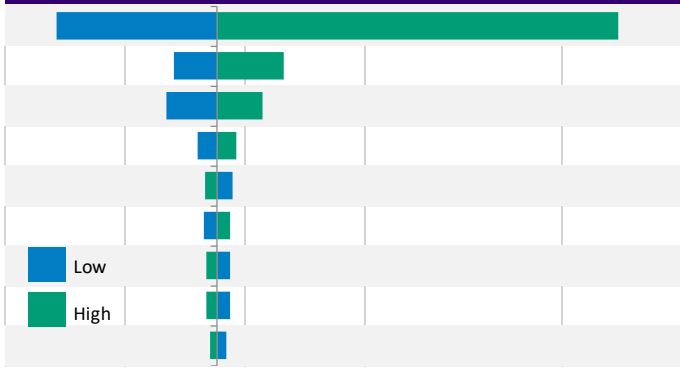
Base-Case Results

Regimen	Cost	LYs	Ambulatory LYs	QALYs
Overall SPMS				
Siponimod	$1,148,000	14.6	5.16	3.41
BSC	$283,000	14.4	4.45	2.66
Incremental	$865,000	0.23	0.71	0.75
ICER	-	**$3,760,000**	**$1,220,000**	**$1,150,000**
Active SPMS				
Siponimod	$714,000	14.7	5.69	2.42
BSC	$307,000	14.4	4.45	1.48
Incremental	$407,000	0.26	1.24	0.94
ICER	-	**$1,570,000**	**$329,000**	**$433,000**

BSC: best supportive care, ICER: incremental cost-effectiveness ratio, LY: life-years, QALYs: quality-adjusted life years, SPMS: secondary progressive multiple sclerosis

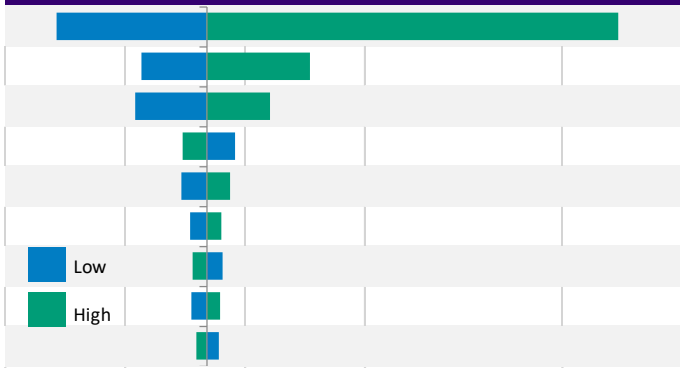
One-Way Sensitivity Analyses

Overall SPMS Population



Parameter	Base case	Low Value	High Value
HR of progression for siponimod	0.79	0.65	0.95
Relapse RR for siponimod	0.450	0.340	0.590
Siponimod list price per 30 days	$7,274	$6,547	$8,001
Proportion of relapses which are mild/moderate	70.8%	63.7%	77.9%
Utility for EDSS 6	0.481	0.433	0.529
Discount rate for outcomes	3.0%	2.7%	3.3%
Discount rate for costs	3.0%	2.7%	3.3%
Annual utility decrement of severe relapse	0.302	0.272	0.332
Annual utility decrement of mild/moderate relapse	0.091	0.082	0.100

Active SPMS Subpopulation

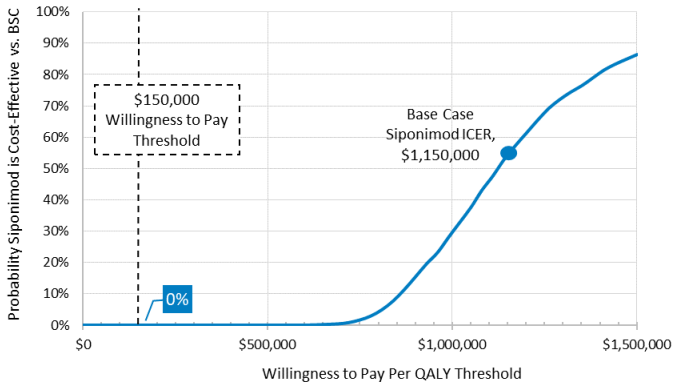


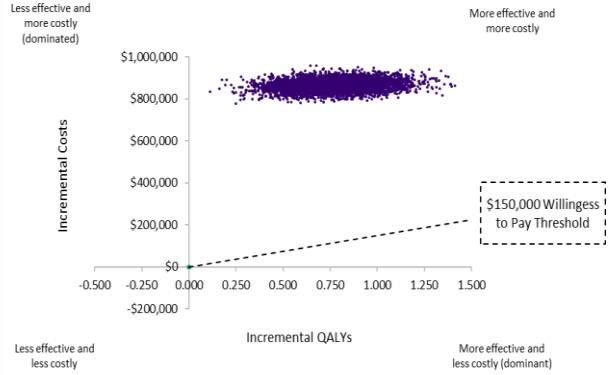
Parameter	Base case	Low Value	High Value
HR of progression for siponimod	0.67	0.49	0.91
Relapse RR for siponimod	0.45	0.34	0.59
Siponimod list price per 30 days	$7,274	$6,547	$8,001
Utility for EDSS 6	0.481	0.433	0.529
Proportion of relapses which are mild/moderate	70.8%	63.7%	77.9%
Mean age at baseline (years)	48.0	43.2	52.8
Annual utility decrement of severe relapse	0.302	0.272	0.332
Discount rate for outcomes	3.0%	2.7%	3.3%
Annual relapse rate for EDSS 6	1.100	0.990	1.210

EDSS: Expanded Disability Status Scale, HR: hazard ratio, RR: risk ratio, SPMS: secondary progressive multiple sclerosis

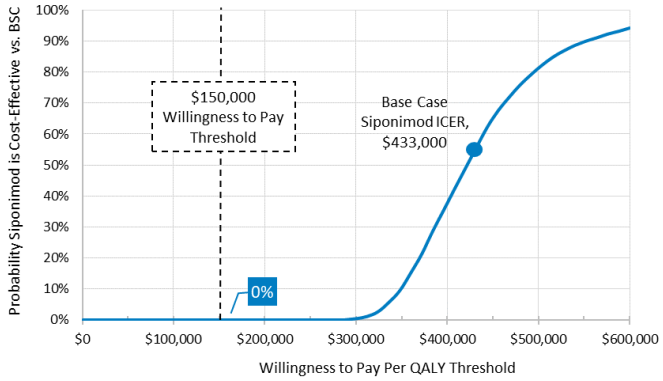
Probabilistic Sensitivity Analysis

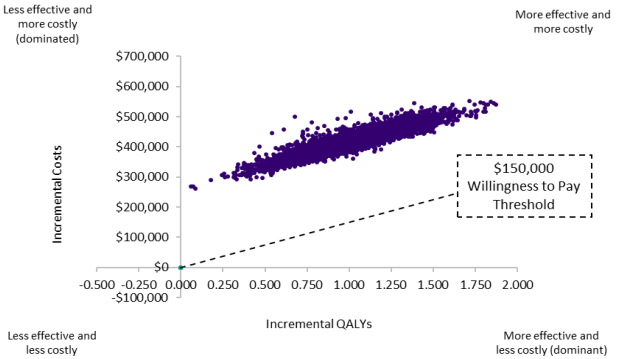
Overall SPMS Population





Active SPMS Subpopulation





BSC: best supportive care, ICER: incremental cost-effectiveness ratio, QALYs: quality-adjusted life years, SPMS: secondary progressive multiple sclerosis

Summary of Scenario Analyses

- Modified societal perspective
  - ↓incremental cost with no impact on QALYs
  - $1.14M per QALY for the overall SMPS
  - $422,000 per QALY in active SPMS
- No other scenarios resulted in cost per QALY results near commonly-accepted thresholds
  - Inclusion of caregiver burden
  - Extend stopping rule to EDSS 8 or 9 in active SPMS
  - Alternative mortality multipliers
  - Alternative utility values
  - Non-active SPMS population

EDSS: Expanded Disability Status Scale, QALYs: quality-adjusted life years, SPMS: secondary progressive multiple sclerosis

Results of Scenario Analysis: MAIC of Siponimod vs Interferon Beta-1b

- Siponimod vs European study of interferon beta-1b using the manufacturer-submitted MAIC[1]
  - High proportion of patients with relapse within 2 years (~70%)
  - Statistically significant benefit for interferon beta-1b vs placebo for time to CDP at 3 months; HR 0.74 (95% CI 0.60, 0.91)
  - MAIC adjusted for differences in age, EDSS, and the proportion of patients with relapse within 2 years
- Results
  - ↓incremental cost but ↓ incremental QALYs
  - Higher ICERs than base case based on interferon net price

1. Kappos L, et al. *Neurology.* 2001;57(11):1969-75.

CDP: confirmed disability progression, CI: confidence interval, EDSS: Expanded Disability Status Scale, HR: hazard ratio, ICER: incremental cost-effectiveness ratio, MAIC: matching-adjusted indirect comparison, QALYs: quality-adjusted life years

Value-Based Price

- Value-based price benchmarks are not provided for siponimod. This report evaluated siponimod as treatment for SPMS. As the FDA-approved indication for siponimod is for relapsing forms of MS, and active SPMS is only a portion of the patients with SPMS and does not include RRMS, we are not providing value-based price benchmarks for siponimod as part of this review.

Limitations

- Natural history data are from an older study
  - May not represent current SPMS populations due to differences in diagnostic and treatment practices
  - Limited information on natural history of active SPMS
- Utility, costs, relapse rates, and efficacy of comparators specific to active SPMS are not available in the literature
- Analysis is not reflective of the full FDA-approved label for siponimod
- Analyses were based on the list price for siponimod

SPMS: secondary progressive multiple sclerosis

Comments Received

• Concerns about modeling active SPMS as defined by relapse in the two years prior to baseline	**Predefined subgroup and aligns with FDA language**
• BSC may not be appropriate comparator in real-world practice	**Insufficient comparative efficacy data**
• Relapse rates used in the draft report may underestimate relapse rates among patients treated with siponimod in clinical practice	**Modification made from the draft report: alternative source of relapse rates**
• Utilities used in the draft report contained negative values for some health states	**Modification made from the draft report: to alternative source of utility values**

BSC: best supportive care, SPMS: secondary progressive multiple sclerosis

Conclusions

- Siponimod improves outcomes compared to BSC
- Using the current list price for siponimod, results were above commonly cited thresholds for cost effectiveness in the base case
  - Unlikely to be cost-effective in the overall SPMS trial population and subpopulation with active disease
  - Cost per QALY gained was above $150,000 for all scenarios explored

BSC: best supportive care, QALYs: quality-adjusted life years, SPMS: secondary progressive multiple sclerosis

Questions?

Backup Slides

Model Cohort Characteristics

- Patients enter the model according to the baseline characteristics of the EXPAND Trial[1]
  - Mean (SD) age of 48 (4.8) years
  - 61% Female

EDSS State at Baseline	Proportion of Patients
1	0.0%
2	0.5%
3	14.0%
4	14.0%
5	16.1%
6	55.3%
7	0.2%
8	0.0%
9	0.0%

1. Kappos L. *Lancet.* 2018;391(10127):1263-1273.

Key Model Inputs: Natural History of SPMS

- Natural History transitions between EDSS states based on data from the London-Ontario cohort[1,2]

		EDSS State at End of Year								
		1	2	3	4	5	6	7	8	9
EDSS State at Start of Year	1	0.769	0.154	0.077	0.000	0.000	0.000	0.000	0.000	0.000
	2	-	0.636	0.271	0.062	0.023	0.008	0.000	0.000	0.000
	3	-	-	0.629	0.253	0.077	0.033	0.003	0.005	0.000
	4	-	-	-	0.486	0.350	0.139	0.007	0.018	0.000
	5	-	-	-	-	0.633	0.317	0.022	0.026	0.002
	6	-	-	-	-	-	0.763	0.190	0.045	0.002
	7	-	-	-	-	-	-	0.805	0.189	0.006
	8	-	-	-	-	-	-	-	0.926	0.074
	9									1.000

1. Mauskopf J. *J Med Econ.* 2016;19(4):432–42.
2. Scalfari A. *Brain.* 2010;133(Pt 7):1914-1929.

Screening and Monitoring

- All patients initiating siponimod undergo genetic screening to identify CYP2C9 metabolic function
- ~1/3 of patients are assumed require first-dose monitoring

	First Year Screening and Monitoring		
	CYP2C9 (HCPCS 81227)	ECG (CPT 93000)	Office Visit (CPT 99215)
Unit Cost	$174.81	$17.28	$147.76
Utilization	1	2*	1*

*Among the 30% of patients with need for expanded cardiac monitoring
CYP2C9: Cytochrome P450 2C9, ECG: electrocardiogram

1. Centers for Medicare and Medicaid Services. 2018 Clinical Diagnostic Laboratory Fee Schedule. Accessed November 30, 2018.
2. Centers for Medicare and Medicaid Services. 2018 Physician Fee Schedule. Accessed November 20, 2018.

Other Inputs: Caregiver Burden

EDSS State	Annualized Caregiver Disutility[1]
1	0.0020
2	0.0020
3	0.0020
4	0.0450
5	0.1420
6	0.1670
7	0.0630
8	0.0950
9	0.0950

1. Acaster S. *BMC Health Serv Res*. 2013;13:346.

Other Scenario Analyses

Scenario	Cost per Additional LY	Cost per LY of Ambulation	Cost per Additional QALY
Modified societal perspective including indirect costs *(overall SPMS population)*	$3,730,000	$1,211,000	$1,138,000
Inclusion of caregiver burden *(overall SPMS population)*	$3,760,000	$1,218,000	$1,219,000
Discontinuation of siponimod at EDSS 8 *(active SPMS)*	$1,750,000	$472,000	$471,000
Discontinuation of siponimod at EDSS 9 *(active SPMS)*	$2,300,000	$620,000	$557,000
Relative risk of disability progression for siponimod based on 6-month timepoint of the EXPAND trial *(overall SPMS population)*	$2,960,000	$948,000	$992,000
Utility values based on Orme 2007 *(overall SPMS population)*	$3,760,000	$1,220,000	$1,080,000
Mortality multipliers by EDSS score from Harding 2018 for EDSS scores 4-9 *(overall SPMS population)*	$1,250,000	$993,000	$1,050,000
Subpopulation with non-active SPMS	$6,360,000	$2,100,000	$3,300,000

Manufacturer Public Comment and Discussion

Manufacturer Public Commenters

Speaker	Title	Affiliation
Gustavo Suarez Zambrano, MD	Lead Medical Director (Multiple Sclerosis)	Novartis
Jennifer Whiteley, EdD, MSc, MA	HEOR Head of Neuroscience and Rare Diseases in US Medical Affairs	Genentech

Public Comment and Discussion

Kathleen M. Costello, MS, CRNP, MSCN
Associate Vice President, Healthcare Access
National MS Society

No conflicts of interest to disclose.

Fred D. Lublin, MD, FAAN, FANA

Saunders Family Professor of Neurology
Director, The Corinne Goldsmith Dickinson Center for MS
Icahn School of Medicine at Mount Sinai

Conflicts of Interest:

- Dr. Lublin has received advisory board or consulting honoraria from Genentech, Roche, Teva, Medimmune, MedDay, GW, EMD Serono, Sanofi, and Celgene.
- The Corinne Goldsmith Dickinson Center receives research support from Novartis, Actelion, Sanofi, Genentech, and MedDay.
- The Center participated in the Phase III study of siponimod, of which Dr. Lublin was not the PI.
- Dr. Lublin has consulted on patent issues for a different drug with attorneys for Novartis.

Amanda Montague, EdM

Vice President of Education & Healthcare Relations

Multiple Sclerosis Association of America

No conflicts of interest to disclose.

Break

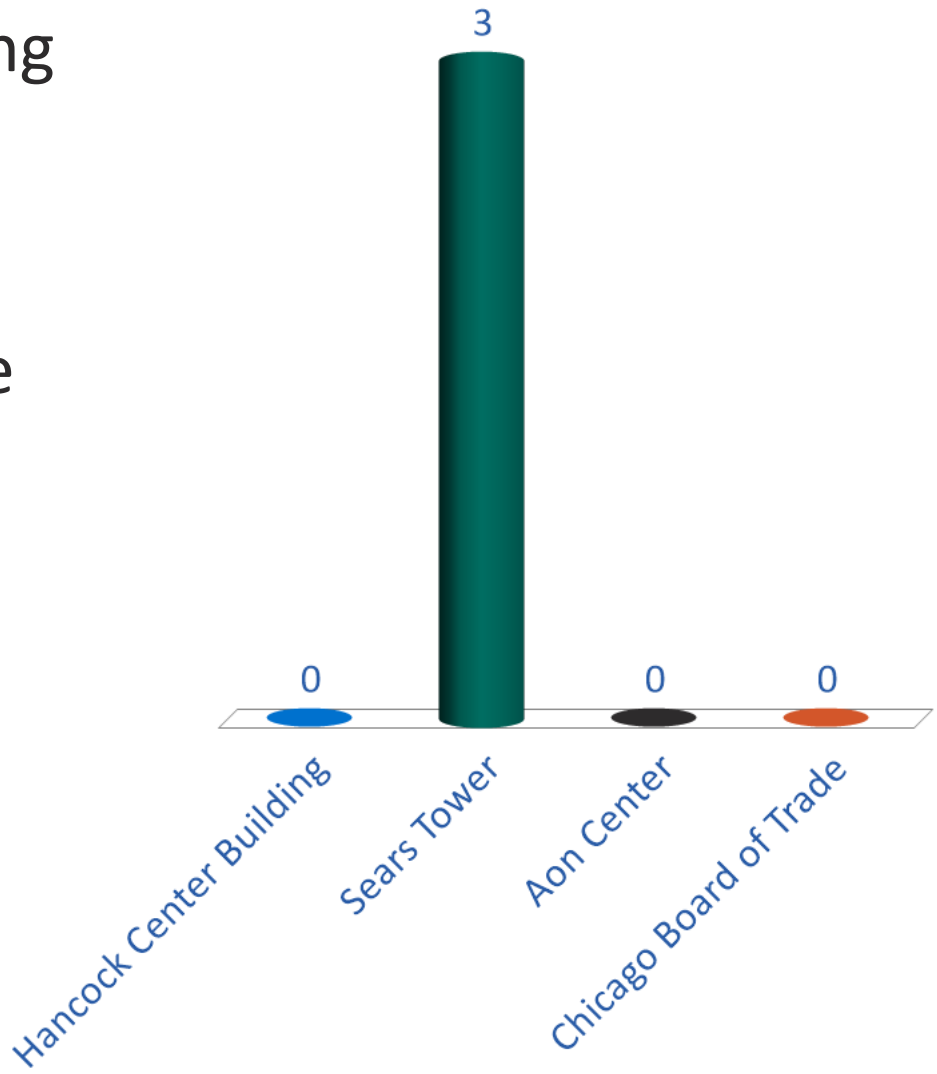
Meeting will resume at 11:00 am

Voting Questions

WiFi Network: @Hyatt_Meetings
Login: ICER19

0. Which skyscraper became the tallest building in Chicago when it was completed in 1973?

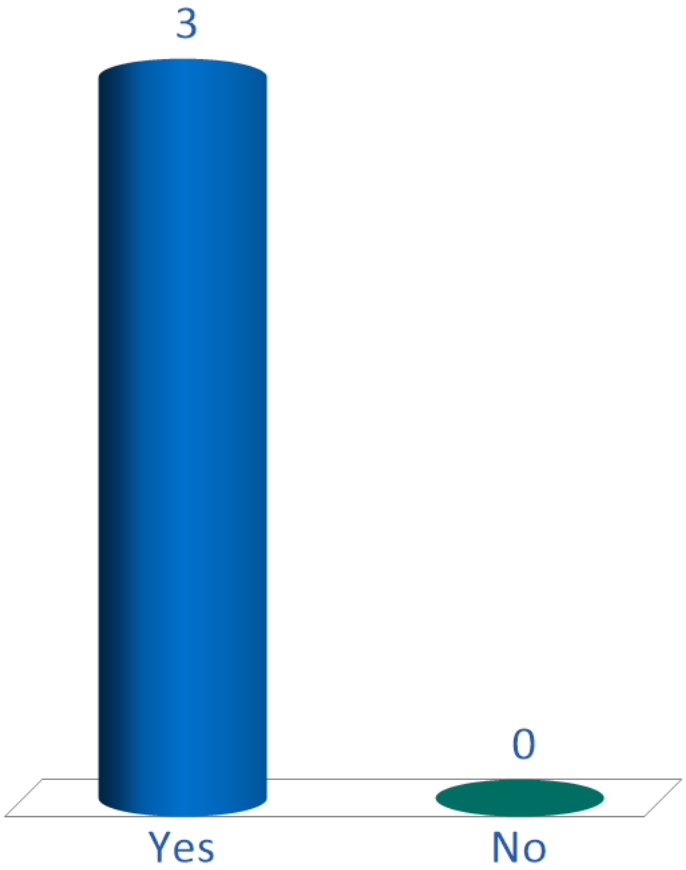
A. Hancock Center Building
B. Sears Tower
C. Aon Center
D. Chicago Board of Trade



1. In patients with ***active*** SPMS, is the evidence adequate to demonstrate that the net health benefit provided by siponimod is superior to that provided by best supportive care?

A. Yes

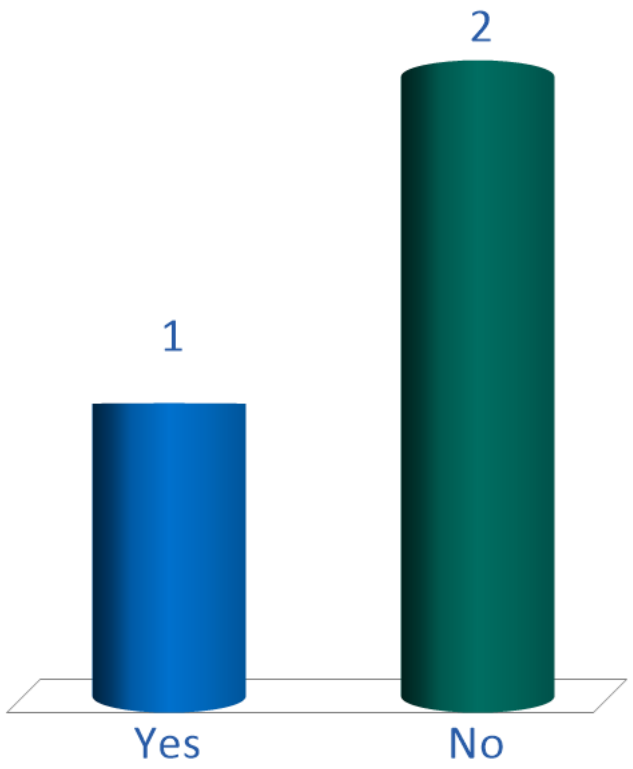
B. No



2. In patients with ***non-active*** SPMS, is the evidence adequate to demonstrate that the net health benefit provided by siponimod is superior to that provided by best supportive care?

A. Yes

B. No



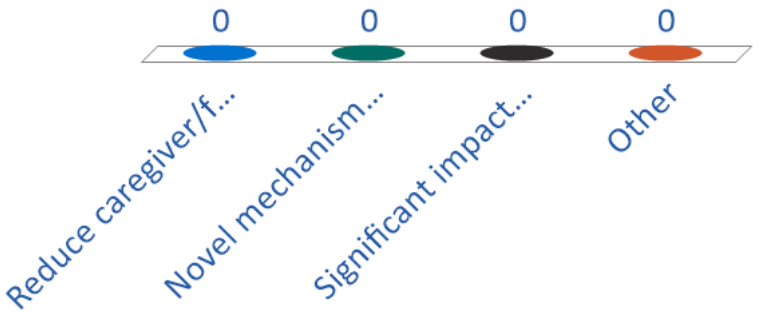
3. For patients with SPMS, does siponimod offer one or more of the following potential "other benefits or disadvantages" versus best supportive care not adequately captured in the clinical trial data or base-case cost-effectiveness model results?"

A. Reduce caregiver/family burden

B. Novel mechanism of action or approach

C. Significant impact on improving return to work/overall productivity.

D. Other



4. For patients with SPMS, are any of the following contextual considerations important in assessing siponimod's long-term value for money versus best supportive care?

A. Care of individuals with condition of high severity

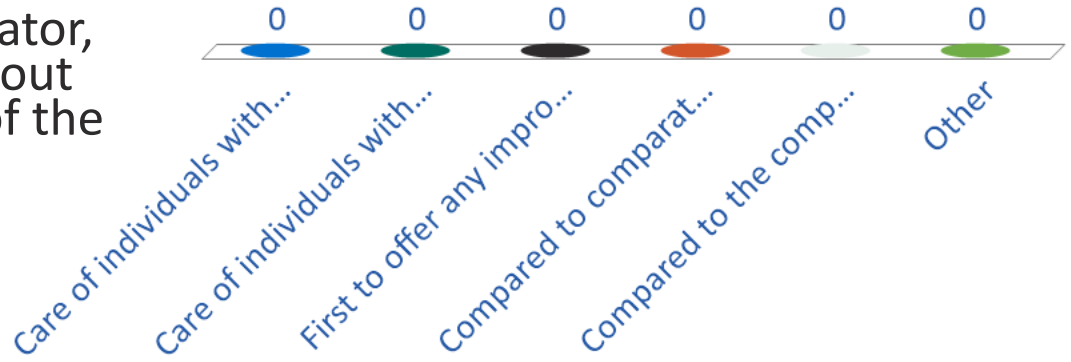
B. Care of individuals with condition with high lifetime burden of illness

C. First to offer any improvement

D. Compared to comparator, there is significant uncertainty about long-term risk of serious side effects

E. Compared to the comparator, significant uncertainty about magnitude or durability of the long term benefits of this intervention

F. Other



Key Policy Discussion

Key Policy Discussion Participants

Participant	Affiliation	Conflicts of Interest
Bruce A. Cohen, MD	Professor, Davee Department of Neurology and Clinical Neurological Sciences, Northwestern University Feinberg School of Medicine	Dr. Cohen has received consulting income from Biogen, Celgene, and EMD Serono and research funding from Roche/Genentech and MedDay. He owns stock in Abbott Laboratories, AbbVie, and CVS Health.
Jeremy Fredell, PharmD, BCPS	Director Trend Solutions – Drug Trend & Formulary, Express Scripts	Dr. Fredell is a full-time employee of Express Scripts.
Annette Langer-Gould, MD, PhD	Regional Lead for Clinical and Translational Neuroscience, Kaiser Permanente/Southern California Permanente Medical Group	No conflicts of interest to disclose
Ann M. Moore	Patient Advocate	No conflicts of interest to disclose
Hollie Schmidt, MS	Vice President of Scientific Operations, Accelerated Cure Project for Multiple Sclerosis	No conflicts of interest to disclose
Gustavo Suarez Zambrano, MD	Lead Medical Director (Multiple Sclerosis), Novartis	Dr. Suarez Zambrano is a full-time employee of Novartis.

Midwest CEPAC Panel Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on or around June 20th
  - Includes description of Midwest CEPAC votes, deliberation, policy roundtable discussion
- Materials available at:

  https://icer-review.org/topic/multiple-sclerosis/

Lunch

Meeting will resume at 1pm