# 080 Evaluation of Real-World Evidence (RWE) in Regulatory and Health Technology Assessment (HTA) Submissions [633]

**Shivani Aggarwal**[1], **David Goldfarb**[2]

[1]Landmark Science, Inc., Los Angeles, CA, USA, [2]Landmark Science, Inc., New York, NY, USA

Scan here for e-poster

**E-poster and supplementary materials** obtained through the QR code or link are for personal use only and may not be reproduced without permission.

## Background & Rationale

- The growing use of real-world data (RWD) and real-world evidence (RWE) in drug development has driven the need for harmonization of guidelines and standards among regulatory authorities and Health Technology Assessment (HTA) bodies.
- Evidentiary standards for RWE vary across regulators and HTA bodies although differences are not well-characterized.
- Regulatory acceptance of MAAs with RWE is well-documented, but its acceptance by HTA bodies remains less clear.
- We compare regulatory and HTA decisions on seven drug marketing applications, analyzing how different regulatory bodies and HTA bodies align or differ in their assessments.

**Objective: to characterize acceptance of the RWE by regulators and HTA bodies for RWE used as either supportive or substantial evidence in MAAs. Through seven examples, we examined whether RWE submitted for regulatory decision-making was accepted across different regulators and HTAs.**

## Methods

### Methods

- We conducted a targeted literature review of regulatory and HTA feedback on drug approvals containing RWE as supportive or substantial evidence in MAAs from January 2021 - present.
- **Regulatory focus**: Food and Drug Administration (FDA) [US], European Medicines Agency (EMA) [Europe], Health Canada (HC) [Canada], & Medicines and Healthcare products Regulatory Agency (MHRA) [UK] due to their significant roles in the regulatory landscape.
- **HTA focus**: NICE [UK], G-BA [Germany], HAS [France], AEMPS [Spain], CADTH [Canada], SMC [Scotland], and TLV [Sweden] provide a comprehensive analysis of HTA reviews of the same RWE.

### Case Study Selection

- We selected **seven medicines** for analysis based on RWE included in their MAA submissions:
  - Idecabtagene vicleucel (ida-cel)
  - Omburtamab
  - Sotorasib
  - Alpelisib
  - Palovarotene
  - Tacrolimus
  - Omaveloxolone
- These were chosen to represent a range of therapeutic areas and evidence types.

### Analysis

- We collected publicly available regulatory reports from sources including the FDA and EMA websites, HTA reports from individual HTA bodies, and summary HTA reports from IQVIA's Market Access Insights®, formerly known as HTA Accelerator.
- Two independent reviewers extracted information on the use and evaluation of RWE.
- We reviewed feedback from regulators & HTA bodies regarding the RWE.

### Categorization & Analysis

- RWE evidence in the MAA was categorized as:
  - **Substantial**: RWE provided the primary data & played a key role in decision-making
  - **Supportive**: RWE provided supplementary evidence in the MAA
- RWE acceptance was categorized as:
  - **Accepted**: RWE accepted based on review
  - **Partially accepted**: RWE accepted but limitations were noted
  - **Not Adequate**: RWE was reviewed and discussed but deemed insufficient and therefore not used/accepted
  - **Not Discussed**: RWE was not addressed or discussed by the reviewing body
- We compared findings across regulatory bodies & HTA bodies to identify patterns of concordance or divergence in RWE acceptance.
- We analyzed common concerns and themes related to the evaluation of RWE.

## Results

**Table 1. Overview of selected medicines and RWE contributing to MAAs**

| Drug | Ide-cel | Omburtamab | Sotorasib | Alpelisib | Palovarotene | Tacrolimus | Omaveloxolone |
|---|---|---|---|---|---|---|---|
| **Manufacturer** | Bristol-Myers Squibb | Y-mAbs | Amgen | Novartis | Ipsen | Astellas | Biogen |
| **Indication** | Relapsed or refractory multiple myeloma | Neuroblastoma with CNS / leptomeningeal metastasis | KRAS G12C+ advanced NSCLC | PI3KCA-related overgrowth spectrum | Fibrodysplasia ossificans progressive | Rejection prevention in lung transplantation | Friedreich's ataxia |
| **Orphan Drug Status?** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Adult or pediatric?** | Adult | Pediatric | Adult | Adult and Pediatric | Adult and Pediatric | Adult and Pediatric | Adult and Adolescents |
| **RWE Study design** | ECA with pivotal Ph2, systematic literature review | ECA with pivotal Ph1 | Retrospective cohort studies, systematic literature review | Retrospective single-arm study | ECA with pivotal Ph3 | Retrospective arm and historical comparator from literature review | ECA with pivotal Ph2 extension |
| **Data Source** | EMR and Registry† | Registry‡ | EMR | Chart review | Chart Review | Registry¥ | EMR |
| **Filing purpose** | First indication | First indication | First indication | Expanded indication* | First indication | Expanded indication* | First Indication |
| **Application type** | BLA | BLA | NDA | NDA | NDA | sNDA | NDA |
| **FDA Approval Date** | Mar 2021 | -- | May 2021 | Apr 2022 | Aug 2023 | Jul 2021 | Feb 2023 |

† Data sources used included clinical sites, Connect® MM Registry, Flatiron, GRN, M2Gen, and COTA. ‡ Central German Childhood Cancer Registry. ¥ Scientific Registry of Transplant Recipients. *Alpelisib and tacrolimus received expanded indications in the U.S. only. NSCLC = non-small cell lung cancer; CNS = Central Nervous System; ECA = External control arm; BLA=Biologics License Agreement; sNDA = Supplemental New Drug Application; NDA = New Drug Application

**Table 2. RWE Acceptance for Seven Medicines Among Four Regulatory Agencies**

| Drug | Ide-cel | | Omburtamab | | Sotorasib | | Alpelisib | | Palovarotene | | Tacrolimus | | Omaveloxolone | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Evidence Type** | Substantial | | Substantial | | Supportive | | Substantial | | Substantial | | Substantial | | Substantial | |
| **Acceptance** | Drug | RWE | Drug | RWE | Drug | RWE | Drug | RWE | Drug | RWE | Drug | RWE | Drug | RWE |
| **FDA (US)** | ✓ | × | × | × | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **EMA (Europe)** | ✓ | ✓ | × | × | ✓ | ✓ | × | × | × | × | -- | -- | ✓ | ✓ |
| **HC (Canada)** | ✓ | -- | -- | -- | ✓ | -- | -- | -- | ✓ | ✓ | -- | -- | ✓ | ✓ |
| **MHRA (UK)** | ✓ | ✓ | -- | -- | ✓ | ✓ | -- | -- | -- | -- | -- | -- | ✓ | ✓ |

FDA = Food & Drug Administration (USA). HC = Health Canada (Canada). EMA = European Medicines Agency (Europe). MHRA = Medicines and Healthcare products Regulatory Agency (UK)

- CADTH accepted RWE for palovarotene as supportive.
- In general, post-hoc propensity-matched analyses for omaveloxolone comparing clinical trial extension data to a global 19-year natural history study was concordant and accepted for regulators and concordant for all HTA bodies (RWE supportive) other than G-Ba (RWE not adequate).
- HTA evaluation of RWE for ide-cel was concordant for G-Ba and HAS (RWE not adequate), and AEMPS and TLV (RWE supportive), while CADTH partially accepted RWE as supportive.
- Common concerns from regulators and HTA bodies included biases from selection of prognostic variables, missingness/incomplete data, study arm comparability, and residual confounding.

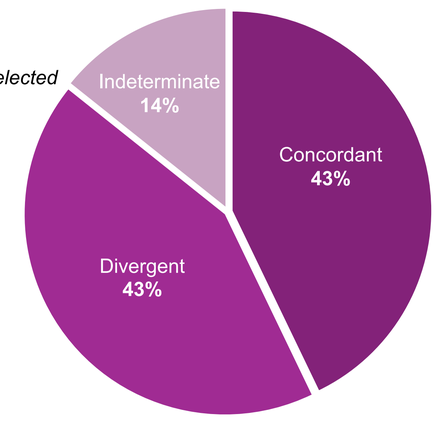
**Figure 1. Regulatory Concordance vs Divergence of the RWE**

**Tacrolimus**
(RWE substantial):
Accepted: FDA
*MAAs not filed in other countries selected*

**Ide-cel**
(RWE substantial):
Rejected: FDA
Accepted: MHRA & EMA
Not discussed: HC

**Palovarotene**
(RWE substantial):
Accepted: FDA & HC
Rejected: EMA

**Alpelisib**
(RWE substantial):
Accepted: FDA accepted
Rejected: EMA




**Sotorasib**
(RWE supportive):
RWE accepted

**Omburtamab**
(RWE substantial):
RWE rejected

**Omaveloxolone**
(RWE substantial):
RWE accepted

**Figure 2. Regulatory Acceptance of RWE by Drug**

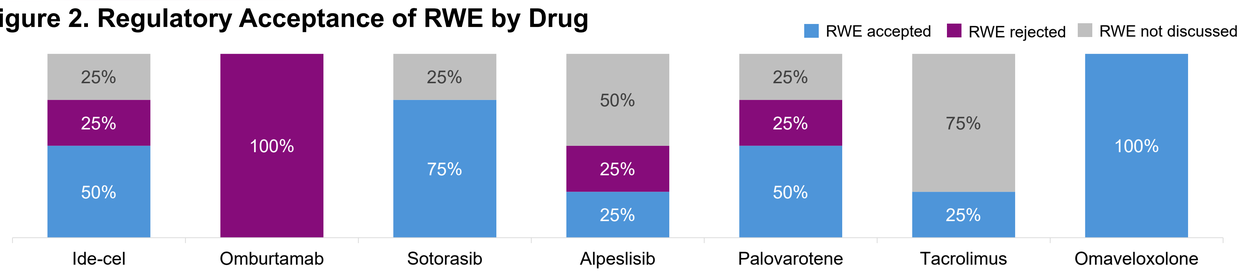
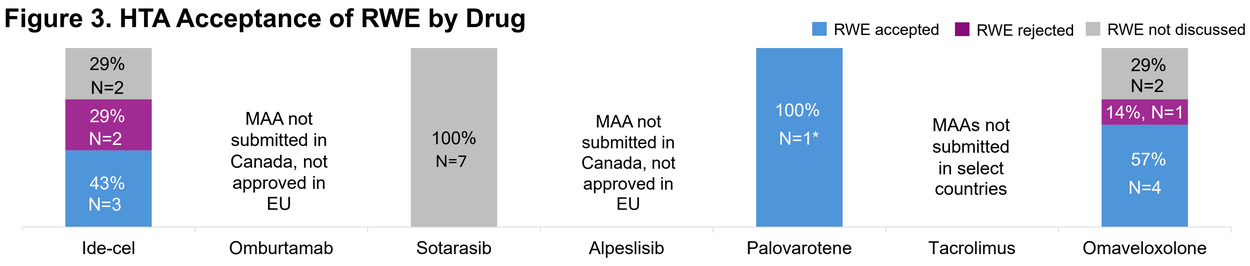



**Figure 3. HTA Acceptance of RWE by Drug**



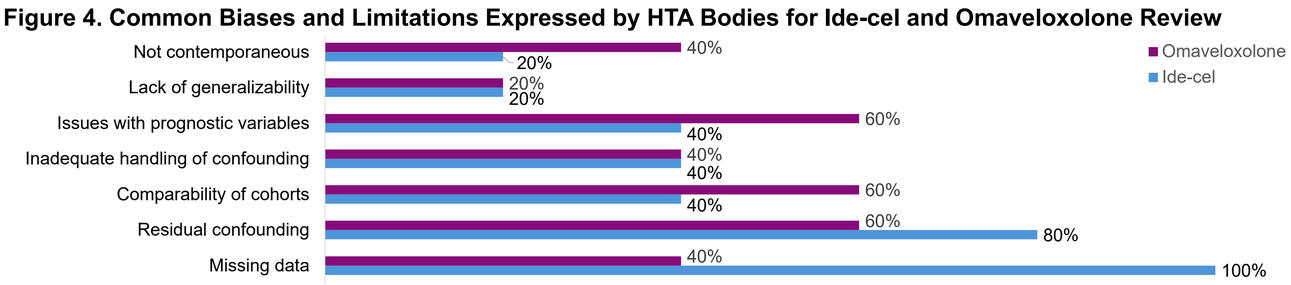

*MAAs not approved in EU

**Table 3. RWE Acceptance for Selected Medicines Reviewed by HTA Bodies**

| Drug | Ide-cel | | | Omaveloxolone | | | Sotorasib | | |
|---|---|---|---|---|---|---|---|---|---|
| **Acceptance** | Drug Reimbursed? | RWE Reviewed? | RWE Accepted? | Drug Reimbursed? | RWE Reviewed? | RWE Accepted? | Drug Reimbursed? | RWE Reviewed? | RWE Accepted? |
| **CADTH (Canada)** | × | ✓ | ✓ | ✓ | ✓ | ✓ | × | × | -- |
| **NICE (UK)** | Review terminated | -- | -- | Review terminated | -- | -- | ✓ | × | -- |
| **HAS (France)** | ✓ | × | × | ✓ | ✓ | ✓ | ✓ | × | -- |
| **G-BA (Germany)** | ✓ | × | × | ✓ | × | × | ✓ | × | -- |
| **AEMPS (Spain)** | ✓ | ✓ | ✓ | --† | ✓ | ✓ | Indeterminate | × | -- |
| **TLV (Sweden)** | × | ✓ | ✓ | No information‡ | ✓‡ | ✓‡ | ✓ | × | -- |
| **SMC (Scotland)** | -- | -- | -- | -- | -- | -- | ✓ | × | -- |

Note: Omburtamab, alpeslisib, tacrolimus, and palovarotene are not presented due to MAAs not being filed and/or submitted in select countries presented here. † No information on reimbursement is available to date from CIMP; data from the positioning report is reported. ‡ No information on the TLV review is available; however, review of the Joint Nordic HTA assessment [~Dec 2024] is presented (jnhb-assessment-skyclarys-omaveloxolone-for-friedreichs-ataxia.pdf).

**Figure 4. Common Biases and Limitations Expressed by HTA Bodies for Ide-cel and Omaveloxolone Review**




Proportions are based on a denominator of N=5, representing the HTAs that reviewed RWE in the ide-cel and omaveloxolone MAAs (CADTH, HAS, G-BA, AEMPS, and TLV).

## Conclusion

- RWE providing supportive or substantial evidence in MAAs was accepted more frequently by FDA than EMA.
- HTA review highlighted differing standards of RWE acceptability. Common types of biases and limitations highlighted by HTA bodies included handling of confounders and prognostic variables, handling of missing data, and residual confounding
- Consideration should be given to these differences when generating RWE for regulatory decision-making and appraisals.
- Select therapies were used as case studies and therefore may not be representative of all treatments and reviews by regulators and HTA bodies.

## Why is this Research Important?

- This project looks at how different regulatory and health authorities handle RWE when approving new drugs. We found that these agencies often have different standards for accepting RWE.
- Companies need to account for these differences when preparing their RWE submissions, tailoring their studies to meet the specific requirements of each body to improve their chances of use and acceptance of the RWE in the submission.

LANDMARK SCIENCE

**References** are available upon request to the corresponding author: Shivani@landmarkscience.com;
**Funding:** This study was funded by Landmark Science, Inc.; **Disclosures**: SA and DG are employees of or are contracted to Landmark Science, Inc.;
**Acknowledgements**: The authors thank Mary Catherine Minnig and Neisha Opper for their assistance with this poster.

**Presented at ISPE 2025 | August 22–26, 2025 | Washington DC**