Characteristics of RWE used in regulatory decision-making for marketing authorization applications

Shivani Aggarwal, PhD, MS[1], David Goldfarb, PhD, MPH[2]
[1]Landmark Science, Los Angeles, CA, [2]Landmark Science, New York, NY
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Background

- RWE is increasingly used to support regulatory decision-making.
- Numerous regulatory agencies including the FDA and EMA have issued guidance on evaluating RWE in MAAs, yet trends in its application in MAAs are not well characterized.

Objective: to characterize trends of RWD/RWE and regulatory feedback on drug submissions containing RWE in MAAs

RWD = real-world data, RWE = real-world evidence

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Methodology

- We examined trends in RWE use and regulatory feedback on drug submissions containing RWE in MAAs from January 2021 to present.
- Publicly available regulatory reports from the FDA were extracted and reviewed for MAAs containing RWD/RWE.
  - Multidisciplinary reports were obtained by querying the Drugs@FDA database.
  - Reports were reviewed for the RWE submitted and for regulatory feedback of the RWE.
  - Where available, FDA DEPI reports were extracted and reviewed.

DEPI = Division of Epidemiology. Drugs@FDA: FDA-Approved Drugs

Methodology (continued)

- Two independent reviewers extracted and synthesized the reports.
- Focus areas included therapeutic areas, type of RWE, study design and methods employed, and common practices in submissions.
- Descriptive analyses were performed to identify trends in the characteristics of drugs and of the RWE.

7 assets were chosen to represent a range of therapeutic areas, RWE types, and acceptance

Drug	Ide-cel	Sotorasib	Tacrolimus	Alpelisib	Omburtamab	Omaveloxolone	Palovarotene
Indication	Relapsed/ refractory MM	KRAS G12C+ adv/metastatic NSCLC	Rejection prevention for lung transplant	PI3KCA-related overgrowth spectrum (PROS)	Neuroblastoma with CNS/ leptomeningeal metastasis	Friedreich's ataxia	Fibrodysplasia ossificans progressive (FOP)
Date Submitted	Jul 2020	Dec 2020	Dec 2020	Oct 2021	Mar 2022	Mar 2022	Feb 2023^
Approval	Mar 2021	May 2021	Jul 2021	Apr 2022	--	Feb 2023	Aug 2023
RWE Study Design	ECA	Retrospective cohort studies	Retrospective cohort study	Retrospective single-arm study	ECA	ECA	ECA
Data Source	EMR and Registry	EMRs	Registry	Chart review of EMRs	Registry	EMRs	Chart review of EMRs

^ Complete response letter issued Dec 2022 with MAA resubmitted Feb 2023.
CNS = central nervous system, MM = multiple myeloma, NSCLC = non-small cell lung cancer, SLR = systematic literature review.

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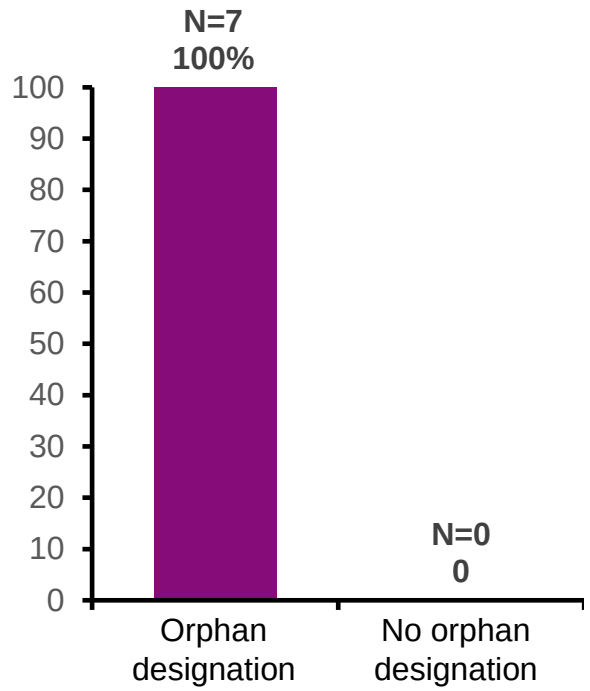
All drugs were for orphan indications, heme/onc or rare indications, and majority were for first indications

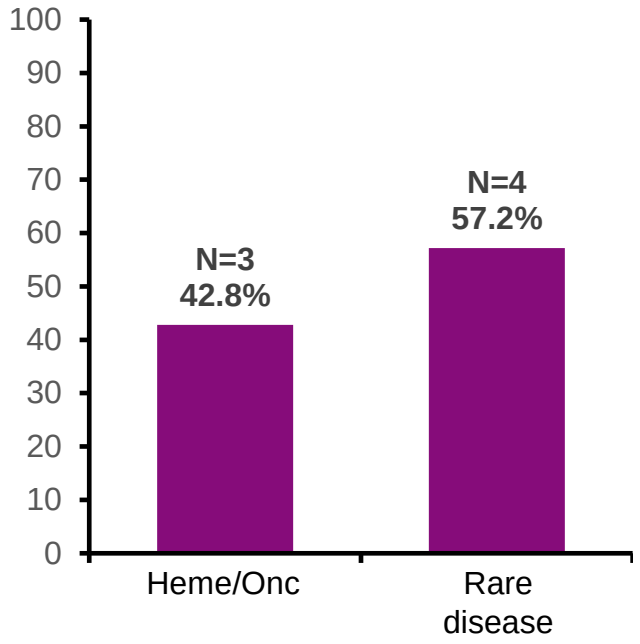
Orphan Designation

All 7 medicines had orphan drug designations and were rare or ultra rare (for example, FOP with ~800 patients globally).



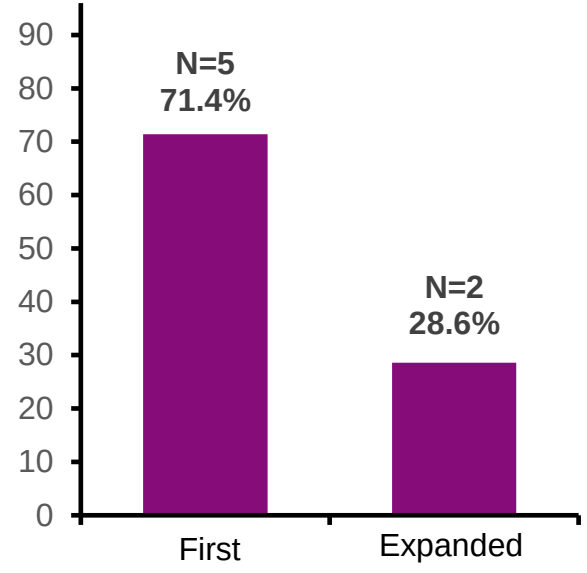
Indication

Heme/Onc	Rare disease
Ide-cel	Tacrolimus
Sotorasib	Alpelisib
Omburtamab	Palovarotene
	Omaveloxolone



First vs expanded indication

First	Expanded
Ide-cel	Tacrolimus
Sotorasib	Alpelisib
Omburtamab	
Palovarotene	
Omaveloxolone	



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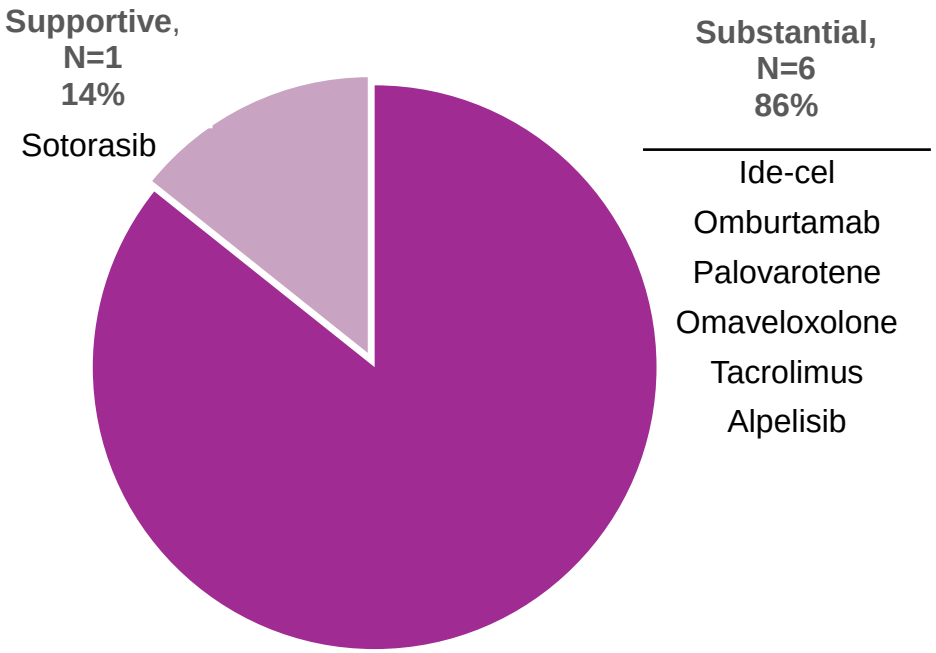
Type of RWE Used

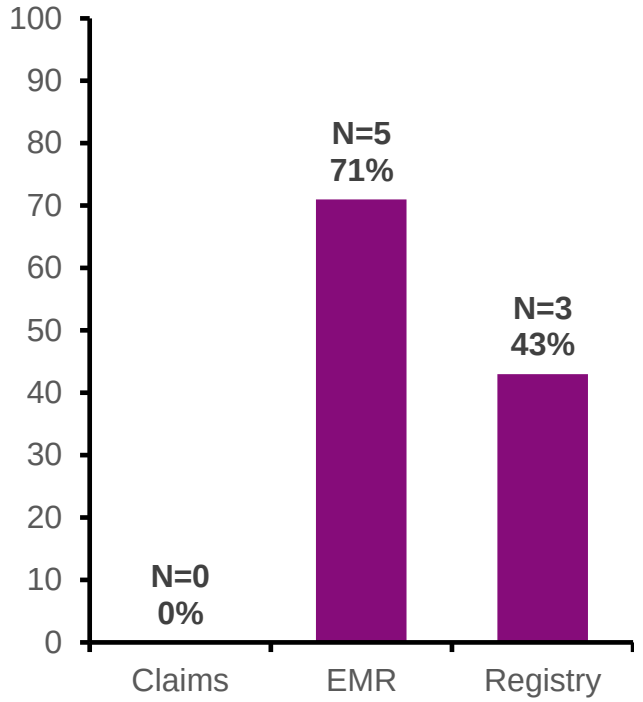
Substantial vs Supportive

- **Substantial**: RWE provided the primary data & played a key role in decision-making
- **Supportive**: RWE provided supplementary evidence in the MAA



RWD Source

- **Claims**
- **Electronic Medical Records**
- **Registry**



EMR	Registry
Ide-cel*	Ide-cel*
Sotorasib	Tacrolimus‡
Alpelisib	Omburtamab¥
Palovarotene	
Omaveloxolone	

***** Submission utilized RWD from multiple data sources including EMR and registry: clinical sites, Connect® MM Registry, Flatiron, GRN, M2Gen, and COTA.
‡ Scientific Registry of Transplant Recipients.
¥ Central German Childhood Cancer Registry.

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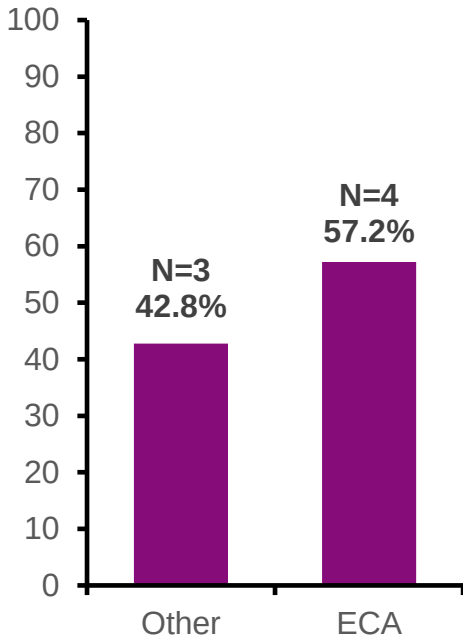
Study Design

Other	ECA
Sotorasib – retrospective natural history	Ide-cel, w/ pivotal Ph2
Alpelisib – retrospective single-arm study	Omburtamab, w/ pivotal Ph1
Tacrolimus – retrospective arm & historical comparator	Palovarotene, w/ pivotal Ph3
	Omaveloxolone, w/ pivotal Ph2



MAAs for expanded indications had reliance on RWE:

- **Alpelisib**

Retrospective single-arm cohort of PROS patients ≥2 years from compassionate use program in multiple countries.

- **Tacrolimus**

Non-interventional study evaluating tacrolimus in routine clinical care using the STRT registry

ECA Acceptance

Two of the 4 ECAs were accepted by the FDA, of which, of which one was post-hoc. Both provided confirmatory evidence.

- **Omaveloxolone**

Post hoc, propensity-matched analysis comparing clinical trial extension study data to a global 19-year natural history study.

- **Paloveretene**

Propensity-matched analysis comparing the single-arm Ph 3 to RW patients from a natural history study, comprised of FOP patients from sites, all of which were also used in the Ph3 study.

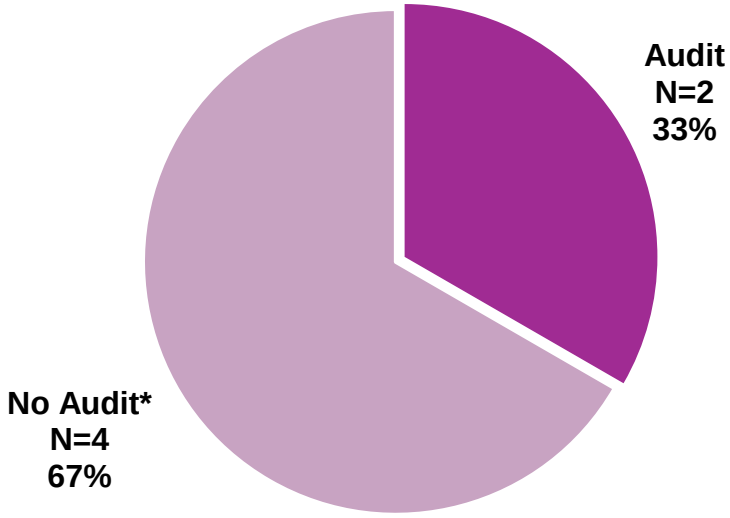
Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, December 2019.
https://www.fda.gov/regulatory-information/search-fda-guidancedocuments/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products

Reproducibility and Transparency

Audit or inspection

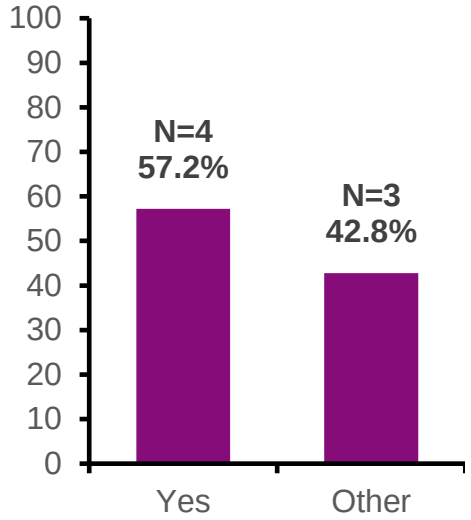
FDA audit or site inspections for sites contributing to raw RWD were noted in 2 reviews:

- Omburtamab
- Alpelisib



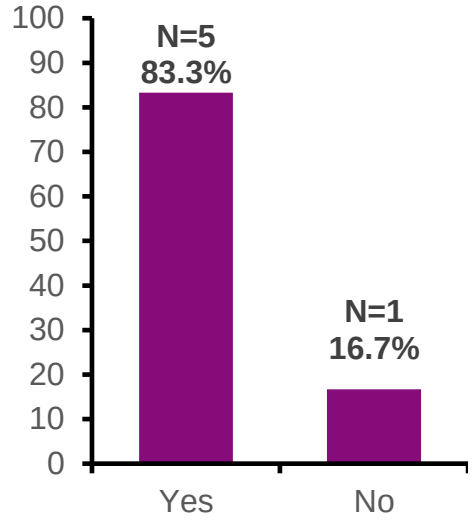
FDA analysis of Patient Level Data

Yes	Other
Alpelisib	Sotorasib – no mention
Tacrolimus	Omaveloxolone – no mention
Omburtamab	Ide-cel^ – not conducted/ used
Paloveretene	



Protocol/SAP Predefined†

Yes	No
Alpelisib	Omaveloxolone
Tacrolimus	
Omburtamab	
Ide-cel	
Paloveretene	



PLD = patient level data. * For tacrolimus, FDA review team did not request inspections by Office of Scientific Submissions for the tacrolimus submission due to the rigor of the regulatory oversight of the SRTR. ^ PLD was submitted for ide-cel. † Data unavailable for sotorasib based on regulatory documents.

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Summary of Drug and RWE Approvals

Drug	Ide-cel	Sotorasib	Tacrolimus	Alpelisib	Omburtamab	Omaveloxolone	Palovarotene
RWE Study Design	ECA, SLR	Retrospective cohort studies, SLR	Retrospective cohort study	Retrospective single-arm study	ECA	ECA	ECA
Data Source	EMR and Registry	EMR	Registry	Chart review of EMRs	Registry	Registry	Chart review of EMRs
Approved by FDA?	✓	✓	✓	✓	No	✓	✓
RWE included in review?	No	✓	✓	✓	No	✓	✓

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Strengths

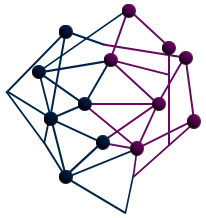
- Included MAAs in which RWE and/or primary clinical evidence for the medicine(s) was not accepted, thus providing variety of case studies.
- Covered a variety of disease areas and types of RWE.
- Relevant to current trends in how RWE may be used in the regulatory space.

Limitations

- This analysis did not systematically review all submissions between 2021 onwards.
- Select drugs submitted to the FDA were used as case studies and therefore may not be representative of all MAAs, such as MAAs using RWE submitted to EMA.

Conclusion

- These reviews highlight varying levels of RWE acceptability.
- MAAs containing RWE submitted to the FDA were for orphan indications and predominantly for first-in-class indications.
- Acceptability of RWE varied based on entire body of evidence, including disease, suitability and robustness of RWE, and appropriateness of RWE as confirmatory evidence.



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Thank you

Questions?

Please email shivani@landmarkscience.com

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