How to Use Real-World Data Across Regions to Gain Regulatory Approval: A Case Study

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Poster # IC6

PROBLEM STATEMENT

A new MAA received a negative opinion from the CHMP. Two study sites were considered to have serious issues with conformance standards to Good Clinical Practice guidelines. Excluding data from the sites rendered the primary endpoint nonsignificant. The manufacturer could not conduct another trial.

Regulatory Challenge: A Case Study

MAA submission: 2015

Only **one pivotal study** BA058-05-003 (ACTIVE) (NCT01343004)[1]

Data exclusion (2 sites) due to Good Clinical Practice-related concerns

Primary endpoint was rendered **nonsignificant**

MAA negative opinion: March 2018

ACTIVE trial[1]	Abaloparatide (N=824)	Placebo (N=821)
KM estimate NVF event rate (%) (95% CI)	2.7 (1.7, 4.3)	4.7 (3.4, 6.6)
- HR (95% CI)		0.57 (0.32, 1.00)
- *P* value		0.049
ACTIVE trial (excluding 2 sites)	**Abaloparatide (n=688)**	**Placebo (n=696)**
KM estimate NVF event rate (%) (95% CI)	2.7 (1.6, 4.4)	3.6 (2.3, 5.4)
- HR (95% CI)		0.74 (−0.38, 1.43)
- *P* value		NS

Evidence Required for Regulatory Approval

Evidence Gap: Treatment Efficacy

- Efficacy in reduction of NVF: ABL vs PBO

Efficacy Evidence Required

- Demonstrate the efficacy of ABL in reducing the risk of nonvertebral fractures compared to placebo in PMO

Evidence Gap: Treatment Safety

- ABL use was associated with transient and reversible increases in heart rate.
- No published epidemiological studies were conducted to examine the CV risk associated with transitory, intermittent increases in heart rate due to an external intervention in the target population of PMO.

Safety Evidence Required

- Safety of ABL vs PBO in MACE in PMO

APPROACH

Description: This is a case study featuring the use of US real-world data to secure the approval of a new drug in Europe. The revised medical marketing authorization incorporated data from one pivotal clinical trial, data from the FAERS database, and a US effectiveness and cardiovascular safety study. The execution of a robust real-world study in this instance addressed a critical data gap, ultimately leading to the EU approval.

Approach: Scientific Advisory Meetings to Inform Research Plan

Advisory Meetings With 8 Countries

- Accepted availability of significant data supporting abaloparatide's anabolic effect on the bone
- Discussed the conduct of a second RCT would not be feasible or ethical
- Supported submission of a new MAA and RWE as an important component of the dossier
- **Justification was made to use RWE given the totality of evidence available from US data**

RWE Generation Plan

- Prespecified protocol and analysis plan
- Power calculation
- Propensity score matching
- Recommended mortality data
- Subgroup analyses of high-risk patients
- Note the strengths and limitations
- Describe why US patients are relevant for the EU population

Figure 1. Timelines for Submission and Approval of the MAA for Abaloparatide in US and EU[2]

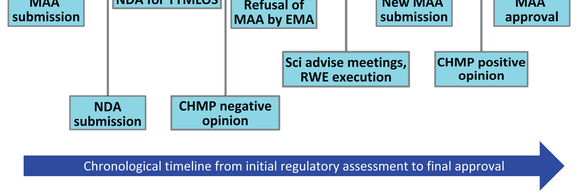

Figure adapted from Davenport C et al. *Ther Innov Regul Sci* 2024;58:505–18 under CC BY license.

Considerations for Use of RWE Across Regions: US vs EU

- Target Populations:
  - Are the target populations for the drug comparable across regions in their baseline risks?
- Clinical Practice Guidelines:
  - Is the condition treated in a similar manner across regions?
- Market Access:
  - Will patients have comparable access to the new vs old drug?
- Patient Behaviors:
  - Are patients expected to adhere the same way to the medication in EU vs US?

New Efficacy and Safety Data Considered and Gained Approval Without 2nd Randomized Control Trial

Effectiveness Data Gaps Addressed

Retrospective observational study (BA058-05-028)

Phase 3 Japanese bridging study (ITM-058-301)

Histology (bone biopsy data to support MOA)

New post hoc analysis from ACTIVE demonstrating increased hip BMD relative to TPTD

Safety Data Gaps Addressed

- **Retrospective observational study demonstrated comparable safety on composite endpoints (MACE w/ or w/o heart failure) was comparable to TPTD**
- No safety signals for CV events in completed phase 3 studies
- No safety signals in postmarketing surveillance data in US 947,618 patient-years of treatment
- FAERS did not demonstrate CV risk for abaloparatide.

LESSONS LEARNED

This example demonstrates how data from a real-world study together with other evidence can be used cross-regionally in lieu of an additional RCT when conducting a study is not logistically or ethically feasible.

Key Takeaways

- RWE studies are not meant to replace RCT.
- RWE can be used as supportive information when a RCT is not possible or is unethical to conduct.
- Although RWE is not available prior to drug approval, data from countries where approval has been granted can be used to secure regulatory approval in the targeted market, as demonstrated in the current case study.
- Engage your audience early.
- Must adhere to guidelines from regulators, including a **prespecified protocol and analysis plan**, power calculation, consideration of biases related to assessment of exposure, outcomes and confounders, and **transparency** (register trial).

Please scan the QR code to access supplemental tables and related study articles

Study BA058-05-028: Comparative Effectiveness and Cardiovascular Safety of Abaloparatide and Teriparatide in Postmenopausal Women New to Anabolic Therapy[3]

Study Design: Retrospective observational cohort study

Source: Anonymized US patient claims data from PRA Health Science's Symphony Health Integrated Dataverse®, including enhanced hospital data (**NCT04974723**)

Approach: Propensity score matching used to make sure patients in two cohorts were comparable in their probability to receive and benefit from treatment. An extensive list of indicators of disease severity for both PMO and CV events, including prior history of fractures and treatment history as per evidence-based practice guidelines, considered

Population: 11,616 patients in both ABL and TPTD groups

Follow-up period: 18 months postindex treatment initiation with a maximum of 19 months (consistent with the pivotal phase 3 ACTIVE study)

Study Analyses

Primary Endpoint

- Time to first NVF within 18 months plus 30 days follow-up after treatment initiation

Secondary Endpoint

- Time to first composite endpoint of MACE (nonfatal MI, nonfatal stroke, or hospital CV death) with or without heart failure within 18 months after treatment initiation (while on therapy) plus 30 days follow-up

Exploratory Endpoint

- Time to the first hip fracture within 18 months plus 30 days follow-up after treatment initiation

Propensity Score Matching

- A greedy matching algorithm with no replacement was adopted (caliper width equal to 0.20 times the standard deviation of the logit of the propensity)
- Cohorts were prospectively specified to match on 73 variables (age, prior fracture history, chronic comorbidities, and prior osteoporosis medications)

Statistical Analysis

- A Cox proportional hazards model was used to compare NVF reduction and CV safety between cohorts

RWE Components: The Study Provides Additional Information on Real-World Use and Outcomes in Patients Beyond the RCT

- Following 18 months of treatment, ABL was **noninferior[a] to TPTD in clinical effectiveness: time to first NVF**
  - 335 patients in the ABL cohort and 375 in the TPTD cohort had an NVF (HR [95% CI]: 0.89 [0.77, 1.03])
  - 121 and 154 patients in the ABL and TPTD cohorts sustained a hip fracture (HR [95% CI]: 0.78 [0.62, 1.00])
- Following 18 months of treatment, **ABL was comparable to TPTD in CV safety: time to first cardiovascular event**
  - MACE (HR [95% CI]: 1.00 [0.84, 1.20])
  - MACE + heart failure (HR [95% CI]: 1.05 [0.93, 1.19])

[a]Noninferiority for ABL vs TPTD was established since we demonstrated that the upper bound of 2-sided 95% CI of the HR was 1.03 (less than the prespecified 1.3).

Study Strengths and Limitations[4,5]

Strengths

- In the absence of randomization, propensity score matching was used to make sure the two cohorts were comparable in probability of receiving and benefitting from treatment.
- We ensured **sufficient power** and required 8000 matched samples to have 95% power at a 0.5 significance.
- The study included highly specific endpoints, including a **claims-based validated algorithm** to identify **osteoporosis-related fractures** and a **claims-based validated algorithm** to **derive hospital CV death**.
- For **CV events**, we used **ICD-10-CM codes** for MI, stroke, and heart failure **consistent with the FDA Mini-Sentinel coding** for these events.
- Sensitivity analyses used to test the robustness of findings:
  - Effectiveness evaluation: cumulative and consecutive treatment exposure
  - Safety evaluation: sentinel initiative consideration of CV events in the 183 days prior to CV outcome

Limitations

- Inherent limitations of administrative claims data (ie, BMD values were not available and unknown confounding factors were not adjusted in propensity score matching)
- Compliance (treatment exposure) could not be assessed
- CV events not adjudicated and mortality events outside of hospital not available

Abbreviations
ABL, abaloparatide; ACTIVE, Abaloparatide Comparator Trial in Vertebral Endpoints; AT, as treated; BMD, bone mineral density; CHMP, Committee for Medicinal Products for Human Use; CI, confidence interval; CV, cardiovascular; EMA, European Medicines Agency; EU, European Union; FAERS, FDA Adverse Event Reporting System; FDA, United States Food and Drug Administration; HR, hazard ratio; ITT, intent to treat; KM, Kaplan-Meier; MAA, marketing authorization application; MACE, major adverse cardiovascular event; MI, myocardial infarction; MOA, mechanism of action; NDA, new drug application; NS, not significant; NVF, nonvertebral fracture; PBO, placebo; PMO, postmenopausal osteoporosis; RCT, randomized controlled trial; RWE, real-world evidence; TPTD, teriparatide; US, United States.

References
1. Miller PD et al. *JAMA* 2016;316:722–33; **2.** Davenport C et al. *Ther Innov Regul Sci* 2024;58:505–18; **3.** Cosman F et al. *Osteoporos Int* 2022;33:1703–14; **4.** US Food and Drug Administration. August 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug; **5.** Berger ML et al. *Pharmacoepidemiol Drug Saf* 2017;26:1033–9.

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Conflict of Interest Disclosures
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