Inclusion of Patient-Reported Outcome Endpoints in the Summary of Product Characteristics for Non-oncology Drugs Approved by the European Medicines Agency (2018-2022)

Sarah Sauchelli,[1,*] Courtney Levy,[1*] Ari Gnanasakthy,[2] Lynda Doward,[1] Kristina Fitzgerald[3]

*shared first authorship

[1]RTI Health Solutions, Manchester, England, United Kingdom; [2]RTI Health Solutions, Research Triangle Park, NC, United States; [3]AbbVie, Mettawa, IL, United States

OBJECTIVES

1) To review patient-reported outcomes (PRO)–related statements of product value for new non-oncology drugs approved by the European Medicines Agency (EMA) between 2018 and 2022

2) Identify trends in how PROs and PRO endpoints in clinical trials are evaluated by the EMA

CONCLUSIONS

Patient-reported experiences with new non-oncology treatments approved for marketing in Europe and select countries in the European Economic Area are not yet systematically included in documents used to support treatment decision-making

Methodological improvements in the selection, assessment, and analysis of PROs and PRO endpoints are crucial to build confidence in the robustness of clinical trial results

CONTACT INFORMATION: ssauchellitoran@rti.org

REFERENCES: All data were collected from publicly available documents published by the European Medicines Agency (https://www.ema.europa.eu/en/medicines).

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INTRODUCTION

- The EMA encourages use of PRO data to communicate patients' perspectives on the value of a treatment.
- An EMA scientific committee reviews all evidence submitted by a drug manufacturer seeking marketing authorization for a medicine, including any PRO data.
- The evaluation is published in the form of a Public Assessment Report (PAR) and informs approval or rejection for marketing authorization.
- The PAR is also used to determine if PRO-related information about a medicine can be included in the Summary of Product Characteristics (SmPC) and the medicine's package leaflet.
- The SmPC and package leaflet are used during treatment decision-making; they can be used to communicate patients' perspectives and experiences of a new treatment.

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METHODS

- The PAR, SmPC, and package leaflets published by the EMA for therapeutic indications approved for novel non-oncology substances between 2018 and 2022 were examined.
- PRO-related data and PRO measures (PROMs) used in confirmatory studies were identified.
- The EMA's evaluation of the PRO data in confirmatory studies was analyzed using content analysis principles.
- Any PRO-related statements of treatment effect in the SmPC and package leaflet were extracted and categorized.

RESULTS

- 46% of indications had PRO-related statements of treatment effect in the SmPC and/or package leaflet.
- In most cases, the benefit of treatment on PROs was described (Figure 1).

Study Design

- PRO-related statements in the SmPC and/or package leaflet were most frequent where evidence was derived from randomized controlled trials (Table 1).
- EMA concerns related to study design included:
  - PRO results derived from open-label and/or single-arm studies cannot be interpreted with confidence
  - Short duration of the study period
  - Insufficient sample size
  - PRO endpoints described in the protocol were not those analyzed

PROMs

- Most indications with PRO data used at least 1 disease-specific PROM in confirmatory studies to support a PRO endpoint (Figure 2).
- Critical comments on PROM usage included:
  - Lack of evidence to support PROM validation
  - Selected PROM not suitable for the concept of interest or for the trial population
  - Overlap of concepts assessed by PROMs selected

Endpoints

- Endpoints relating to symptoms or symptom burden were the most frequently incorporated in the SmPC and/or package leaflet to describe treatment effect (Table 2).
- PROs assessed as a primary endpoint were always approved for inclusion in the SmPC and/or package leaflet (Table 2).
- EMA provided negative feedback on the interpretability of PRO data when:
  - Study was underpowered
  - Inadequate or lack of adjustment for multiplicity
  - PRO analyses overlooked confounding factors (e.g., rescue medication use)
  - Classification of non-responders was inappropriate
  - Differences between treatment arms were not considered to be clinically meaningful
  - Endpoint was exploratory
  - Too much missing PRO data
  - Post-hoc analyses were used to support PRO-related results

Figure 1. PRO-Related Statements in the SmPC and Package Leaflet Across Indications

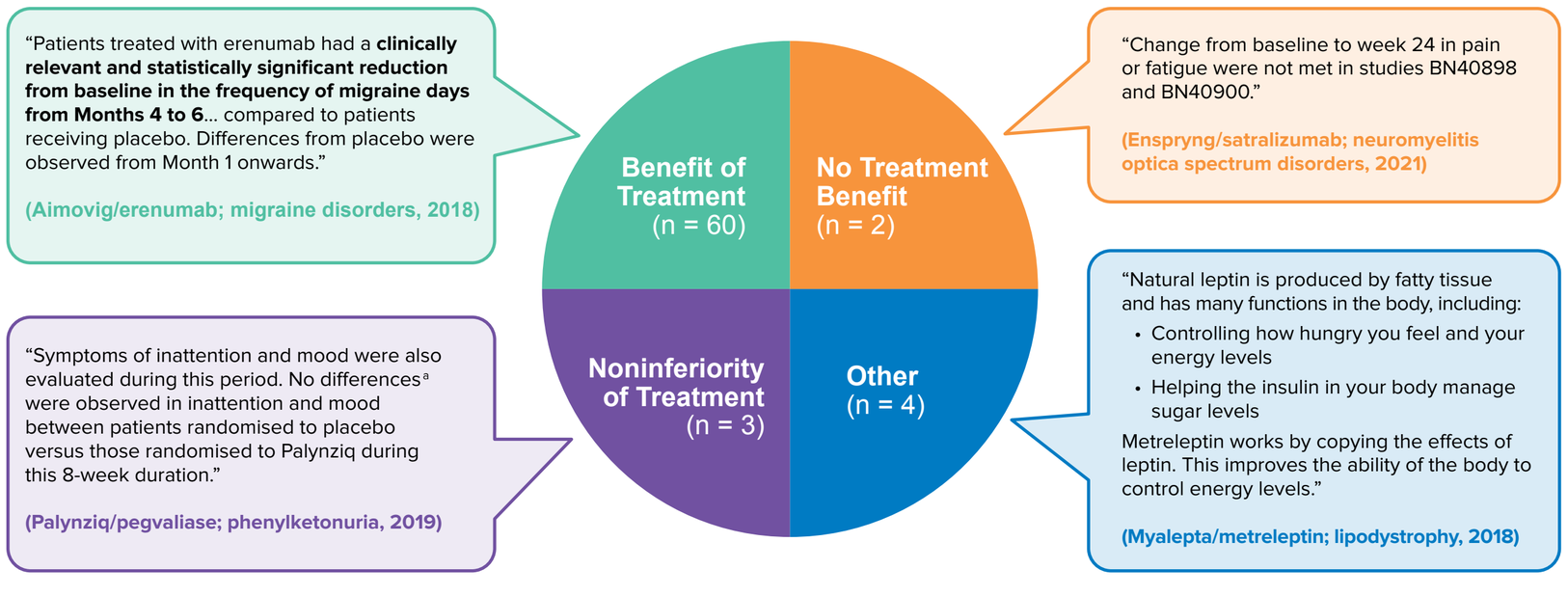


Table 1. PRO-Related Statements in the SmPC and/or Package Leaflet, Across Study Types

Design of confirmatory studies	Indications supported by PRO data, n	Indications with approved PRO-related statements, n (%)
Randomized controlled trial	71	52 (73.2)
Multiple trials with different designs	10	6 (60.0)
Randomized open-label trial	6	3 (50.0)
Single-arm trial	9	1 (11.1)
Mixed design	1	1 (100.0)
Partially randomized, open-label trial	1	0 (0.0)
Total indications	**98**	**63 (64.3)**

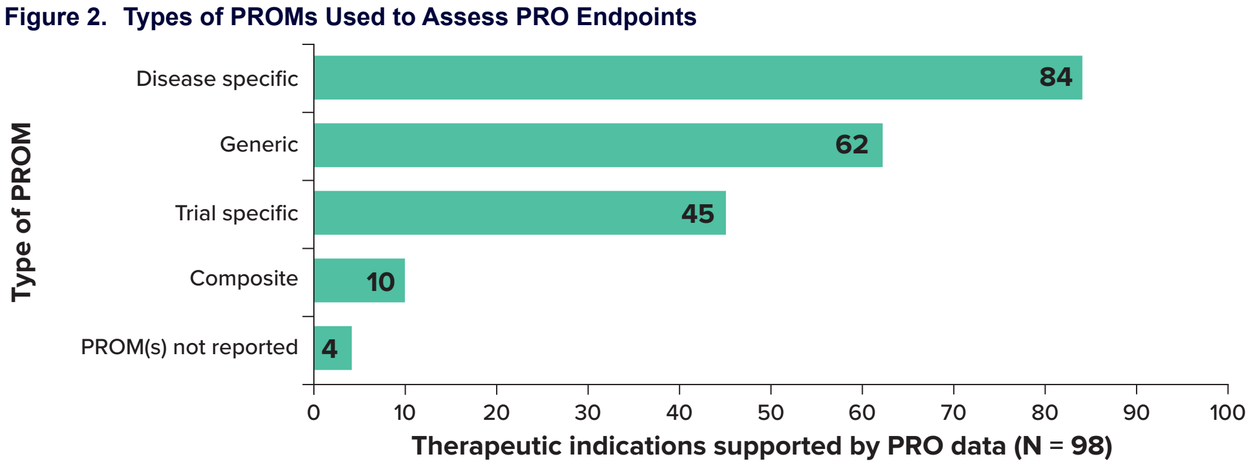
Note: Multiple trials with different designs: open-label eligibility period, a randomized controlled discontinuation trial period, and a long-term open-label extension period.

Table 2. PRO-Related Statements in the SmPC and/or Package, Across Outcome and Endpoint Types

Category	Indications with PRO data, n	Indications with PRO-related statements, n (%)
Placement of PRO-related endpoints		
Primary	24	24 (100.0)
Nonprimary	98	57 (58.2)
Type of concept assessed		
Symptoms or symptom burden	71	56 (78.9)
HRQOL	61	23 (37.7)
Functional status	35	19 (54.3)
Health status	8	3 (37.5)
Patient experience of care	7	0 (0.0)
Total therapeutic indications	**98**	**63 (64.3)**

HRQOL = health-related quality of life.

Figure 2. Types of PROMs Used to Assess PRO Endpoints



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