INDIRECT TREATMENT COMPARISON OF BIOCHEMICAL CONTROL BETWEEN PASIREOTIDE LONG-ACTING RELEASE AND PEGVISOMANT AS SECOND-LINE THERAPIES FOR ACROMEGALY, BASED ON REAL-WORLD EVIDENCE

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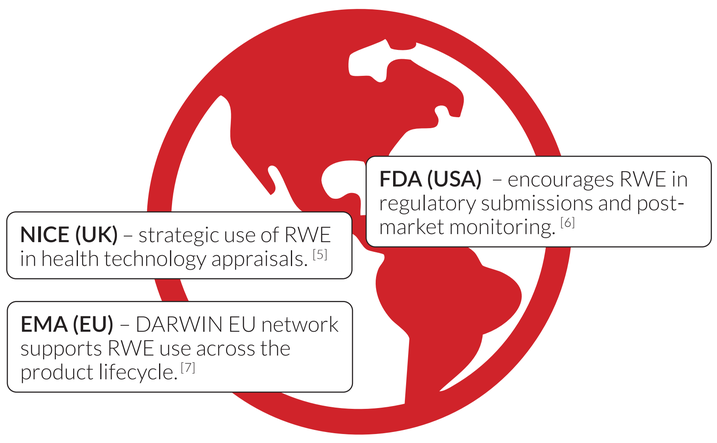
INTRODUCTION

- **Acromegaly is a rare, chronic, progressive endocrine disease**, mostly caused by excessive growth hormone (GH) secretion due to a pituitary adenoma and the resulting hypersecretion of insulin-like growth factor-1 (IGF-1) [1]. Its prevalence is estimated to range from 2.8 to 13.7 cases per 100,000 people, and its incidence from 0.2 to 1.1 cases per 100,000 people per year [2].
- The primary therapeutic objectives in the management of acromegaly are to:
  1. Normalize IGF-1 levels within age- and sex-adjusted reference ranges,
  2. Relieve clinical symptoms,
  3. Reduce tumor size, and
  4. Mitigate the risk of long-term complications [3].
- Recommended first-line medical treatments for acromegaly include first-generation somatostatin receptor ligands (FGSRLs), such as octreotide (OCT) and lanreotide (LAN). Second-line medical options include pegvisomant (PEG), either as monotherapy or in combination therapy with FGSRLs and pasireotide long-acting release (PAS LAR) [4].
- **Both PAS LAR and PEG have demonstrated efficacy and safety in randomized clinical trials. To date there is no direct comparison of both drugs preventing conclusions about their relative effectiveness.**
- Real-world evidence (RWE) is gaining increasing recognition from health technology assessment (HTA) and regulatory agencies [5–7], as it reflects effectiveness in routine clinical practice, and complements RCT data, particularly in rare conditions such as acromegaly.

RWE is gaining **increasing recognition** from HTA and **regulatory agencies**.



Abbreviations: EMA: European Medicines Agency; FDA: Food and Drug Administration, HTA: health technology assessment; NICE: National Institute for Health and Care Excellence; RWE: Real-world evidence

OBJECTIVE

To evaluate the comparative effectiveness assessed through IGF-1 normalization and tumor volume reduction of PAS LAR vs. PEG as second line medical treatments of acromegaly, using real-world evidence.

METHODS

1. Systematic literature review

A systematic literature review (SLR) was conducted in line with standard methodology and the Cochrane Collaboration recommendations [8]. The search was conducted in Medline and Medline In-Process (via PubMed) and in Embase (via Embase). It covered only real-world evidence full text publications available in English, while clinical trials, reviews, meta-analyses, and animal studies were excluded.

Table 1. Systematic literature review inclusion and exclusion criteria

Section	Inclusion criteria	Exclusion criteria
	Adult patients with acromegaly who are unsuitable for or unresponsive to surgery and inadequately controlled with first generation somatostatin receptor ligands.	Patients with Cushing disease, corticotropin-induced adrenocortical hyperplasia, or pituitary ACTH hypersecretion.
	Observational longitudinal studies with or without a comparator group.	Population consisting of less than 10 patients.
	• Pasireotide LAR monotherapy with dosing in line with SmPC. • Pegvisomant monotherapy or combination therapy with dosing in line with SmPC.	Unknown treatment time duration.
	• IGF-1 normalization rate, • tumor volume/diameter, tumor shrinkage/ enlargement rate, • treatment discontinuation due to adverse events, • patient's quality of life.	None.
	Since 2014 pasireotide studies, since 2000 pegvisomant studies.	Before 2014 pasireotide studies, before 2000 pegvisomant studies.

Abbreviations: ACTH: Adrenocorticotropic Hormone; IGF-1: insulin-like growth factor-1; LAR: long-acting release; SmPC: Summary of Product Characteristics.

2. Meta-analysis

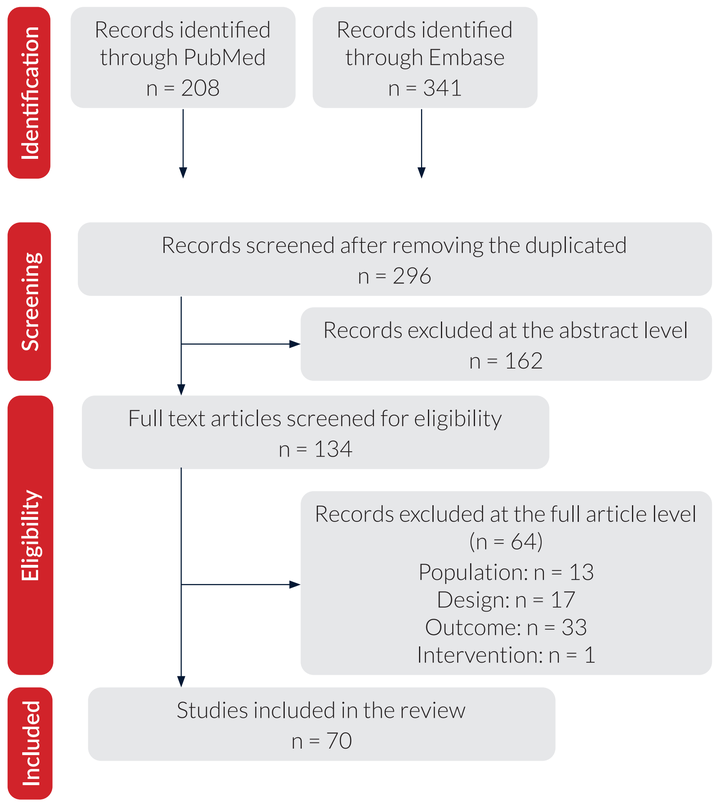
Studies were selected based on the predefined SLR inclusion criteria with treatment durations between 6–24 months to capture the optimal effect of drugs.

Multiple statistical techniques were used to address limitations associated with the analysis of real-world data.

RESULTS

1. Systematic literature review results

Figure 1. PRISMA flow chart of studies selection.



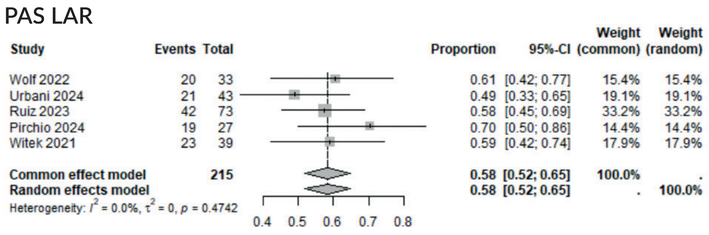
2. Meta-analysis results

A total of 56 studies reported binary IGF-1 normalization outcomes, and 23 studies reported tumor volume reduction. Analyses were conducted across multiple scenarios; only the most clinically relevant results are presented here. **Three scenarios are presented for IGF-1 normalization and one scenario for tumor volume reduction.**

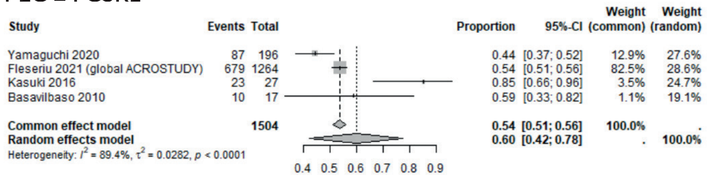
IGF-1 normalization rate

Figure 2. Meta-analysis forest plot including studies reporting outcomes at a strict timepoint (6, 12 or 24 months) are preferred over those reporting median or mean treatment durations. **Populations are adjusted with respect to the proportion of patients after radiotherapy and or surgery (Scenario 1).**

PAS LAR



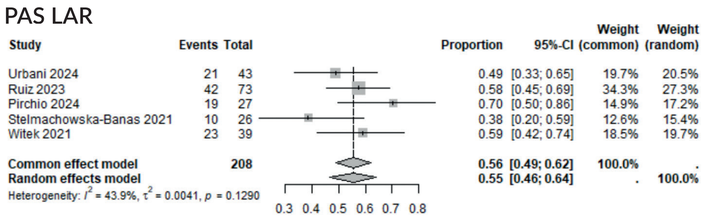
PEG ± FGSRL



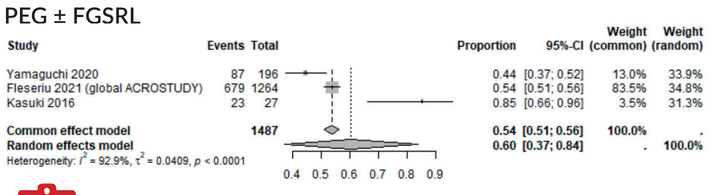
IGF-1 normalization rate PAS LAR: 0.58 [0.52; 0.65]
IGF-1 normalization rate PEG: 0.60 [0.42; 0.78]
Odds ratio: 0.82 (p-value = 0.17)

Figure 3. Meta-analysis forest plot including **only studies reporting outcomes at a strict timepoint. Studies reporting results for PEG monotherapy are excluded (Scenario 2).**

PAS LAR



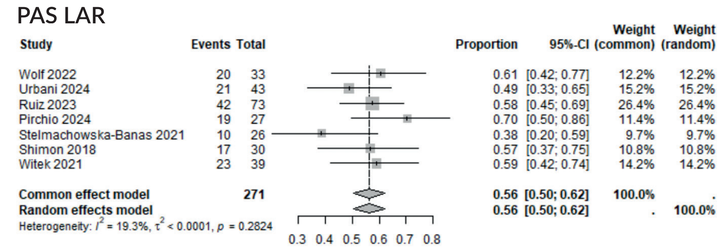
PEG ± FGSRL



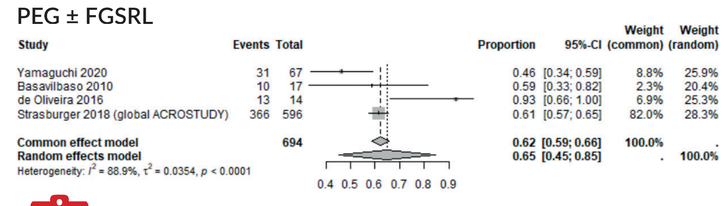
IGF-1 normalization rate PAS LAR: 0.56 [0.49; 0.62]
IGF-1 normalization rate PEG: 0.60 [0.37; 0.84]
Odds ratio: 1.24 (p-value = 0.09)

Figure 4. Meta-analysis forest plot including studies reporting outcomes at a strict timepoint are preferred over those reporting median or mean treatment durations. **The comparator in this scenario is PEG monotherapy (Scenario 3).**

PAS LAR



PEG ± FGSRL

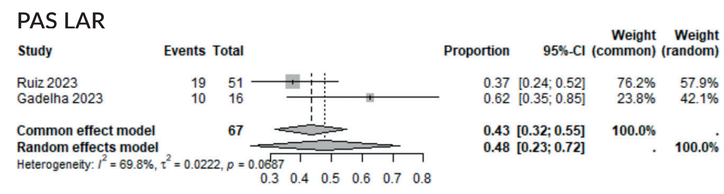


IGF-1 normalization rate PAS LAR: 0.56 [0.50; 0.62]
IGF-1 normalization rate PEG: 0.65 [0.45; 0.85]
Odds ratio: 1.20 (p-value = 0.21)

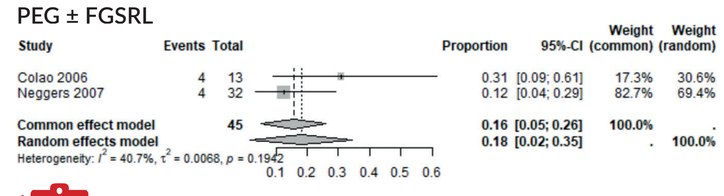
Tumor volume reduction

Figure 5. Meta-analysis forest plot including all studies reporting **tumor volume reduction > 25%**.

PAS LAR



PEG ± FGSRL



Tumor volume reduction > 25% rate PAS LAR: 0.48 [0.23; 0.72]
Tumor volume reduction > 25% rate PEG: 0.18 [0.02; 0.35]
Odds ratio: 0.28 (p-value = 0.005)

ADDRESSING STUDY LIMITATIONS

Real-world evidence studies show substantial heterogeneity in design, populations, outcomes, and treatment durations. Indirect treatment comparisons based on RWE are further limited by the lack of a formal methodological framework.

- Heterogeneity in study design and patient populations was addressed by the I^2 heterogeneity test to quantify variability across, as well as by constructing population-adjusted scenarios to account for baseline differences.
- Variability in clinical outcomes, endpoint definitions, and treatment durations, was mitigated by including only studies with comparable lengths of treatment exposure.
- Lack of standardized guidelines for RWE-based comparisons was addressed by developing multiple scenarios to test the impact of methodological decisions on the robustness of the findings.

CONCLUSIONS

These findings complement well existing RCT evidence. The key results are as follows:

- **Comparable IGF-1 normalization rate:** RWE analyses of IGF-1 normalization are consistent with previous meta-analyses for PAS LAR [9] and PEG [10], **showing similar effectiveness across both treatments, estimated at around 60%**. The results are consistent when considering both PEG monotherapy or combination therapy with FG-SRLs.
- **Tumor shrinkage advantage of PAS LAR:** PAS LAR may provide **greater benefit in reducing tumor size compared to PEG + FGSRLs**, potentially offering an additional therapeutic advantage **(48% vs. 18%; OR =0.28; p =0.005)**.

Additional analyses of alternative scenarios and endpoints are in progress, and the full study findings are intended for submission to a peer-reviewed journal.

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