CO153

# A Feasibility Assessment of an Anchored Indirect Treatment Comparison Between Eneboparatide (CALYPSO) and Palopegteriparatide (PaTHway) in Chronic Hypoparathyroidism

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## INTRODUCTION

- In the absence of head-to-head evidence, an anchored indirect treatment comparison (ITC) of eneboparatide[1,2] versus palopegteriparatide[3,4] was considered using the Phase III CALYPSO and PaTHway trials, respectively.
- Initial screening suggested reasonable alignment across key ITC domains: both trials enrolled adults with hypoparathyroidism (HypoPT), included placebo plus conventional therapy as a nominally common comparator, and applied broadly similar composite-response definitions at similar time points.
- However, differences in protocol-recommended treatment-management frameworks may influence endpoint achievement and the interpretation of comparative treatment effects, warranting a more detailed feasibility assessment.

## OBJECTIVES

- To assess the feasibility of an anchored ITC between eneboparatide and palopegteriparatide, with particular consideration of how differences in treatment-management frameworks may influence response assessment and interpretation of comparative treatment effects.

## METHODS

- Following initial PICOS screening, trial protocols and supporting study materials were reviewed to evaluate potential sources of between-trial heterogeneity across three domains relevant to anchored ITC feasibility and interpretability:
  - Population comparability
  - Treatment-management framework comparability
  - Outcome comparability
- Findings across domains were integrated to assess the feasibility and interpretability of an anchored ITC.

## RESULTS

### Population Comparability

**Table 1. Selected eligibility criteria in CALYPSO and PaTHway**

| Eligibility criteria | CALYPSO | PaTHway |
|---|---|---|
| HypoPT duration | ≥ 12 months | ≥ 26 weeks (~ 6 months) |
| Active vitamin D | Calcitriol ≥ 0.5 µg/day or alfacalcidol ≥ 1.0 µg/day | Calcitriol ≥ 0.5 µg/day or alfacalcidol ≥ 1.0 µg/day[a] |
| Oral calcium dose | ≥ 1000 mg/day | ≥ 800 mg/day[a] |
| Albumin-adjusted serum calcium (sCa) | 7.8 – 9.0 mg/dL<br>Two consecutive measurements ≥1 week apart[b] | 7.8 – 10.6 mg/dL[c] |

**Note:** Selected key inclusion criteria are summarized for comparative purposes. This table does not represent all eligibility requirements or protocol specifications. Refer to the respective study protocols for complete criteria, definitions, and study-specific requirements.

[a]Criteria shown apply to countries other than Japan. In Japan, active vitamin D requirements were calcitriol ≥ 1 µg/day or alfacalcidol ≥ 2.0 µg/day, with no minimum oral calcium dose requirement specified.

[b]Two consecutive measurements ≥ 1 week apart within the specified range, with ≤ 25% change in the daily doses of active vitamin D and oral calcium between measurements.

[c]Ionized sCa 4.40-5.29 mg/dL was also permitted in PaTHway

**Table 2. Selected baseline characteristics in CALYPSO and PaTHway**

| Baseline characteristic | CALYPSO (N=200) | PaTHway (N=82) | ASD[a] |
|---|---|---|---|
| Enrolled in Europe, n (%) | 114 (57.0%) | 31 (37.8%) | 0.39 |
| Age, years, mean (SD) | 51.5 (12.4) | 48.6 (12.7) | 0.23 |
| Postmenopausal, n (% of female) | 78 (50.6%) | 22 (34.4%) | 0.33 |
| HypoPT duration, years, mean (SD) | 13.3 (9.7) | 11.8 (10.7) | 0.15 |
| Albumin-adjusted sCa, mg/dL, mean (SD) | **8.3 (0.6)** | **8.7 (0.7)** | **0.71** |

**Note:** Selected baseline characteristics shown.

[a] ASDs, absolute standardized differences, were calculated to quantify differences in baseline characteristics across study populations. Larger ASDs indicate greater cross-trial imbalance. Bolded values indicate an ASD of ≥ 0.20, the threshold used in this feasibility assessment to identify potentially meaningful differences in baseline characteristics.

### Implications

- Differences in eligibility criteria and selected observed baseline characteristics were identified, resulting in uncertainty regarding population comparability **(Tables 1 and 2).**
- Some observed population differences may be amenable to population-adjustment methods; however, their appropriateness would depend on sufficient population overlap, availability of relevant covariates, and methodological assumptions.

## CONCLUSIONS

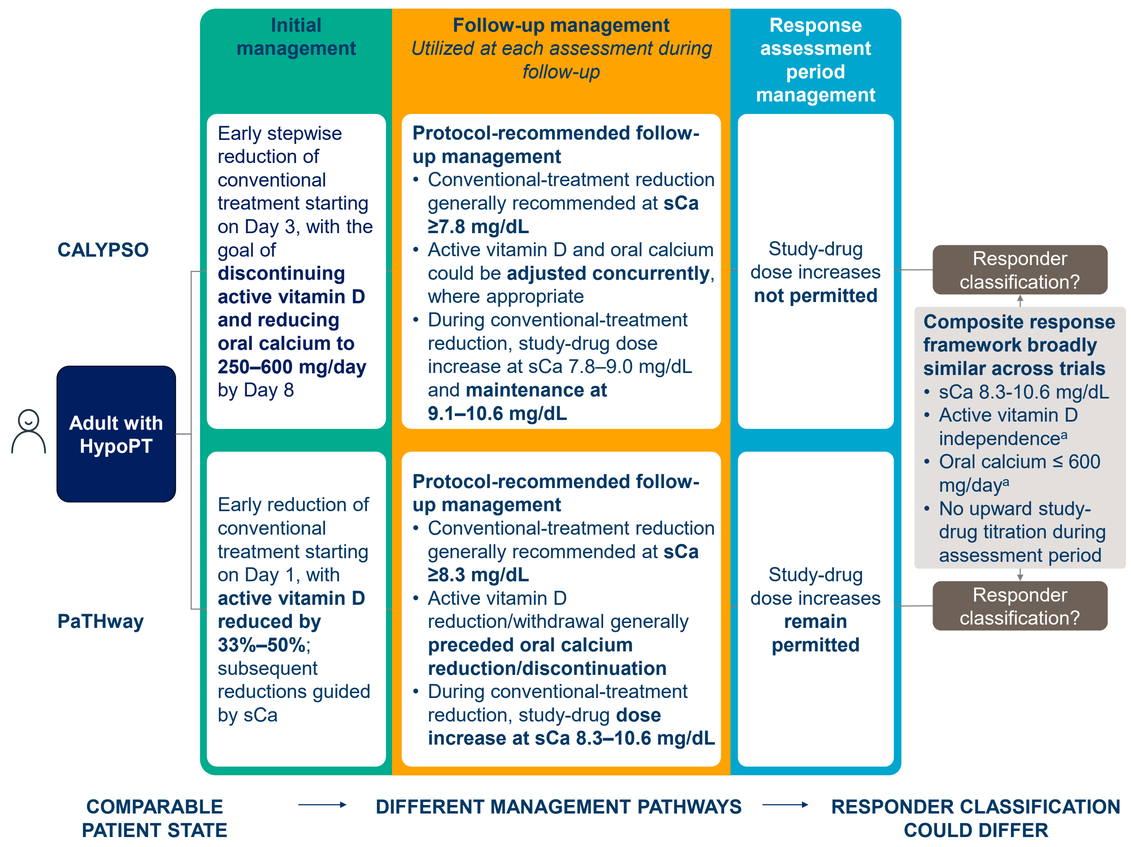
- Differences in eligibility criteria and selected observed baseline characteristics introduced uncertainty regarding population comparability. Some observed differences may be addressable using population-adjusted methods, depending on the characteristics and data available for adjustment.
- However, population adjustment would not address differences in trial-specific treatment-management frameworks, and their impact on observed responses could not be disentangled from the available evidence.
- Accordingly, placebo plus conventional therapy represented a nominal, rather than fully comparable, common comparator because treatment-management frameworks differed between trials, including within comparator arms.
- Consequently, the interpretability of comparative treatment effects could not be established from the available evidence, despite the nominally common comparator and broadly similar composite-response definitions.

## RESULTS (CONTD.)

### Treatment-management framework and outcome comparability

- CALYPSO and PaTHway differed in protocol-specified approaches to conventional-treatment management and study-drug titration during treatment and response assessment.
- Several components of the composite response were directly related to treatment-management decisions, including conventional-treatment use and study-drug titration **(Figure 1).**

**Figure 1. Trial-specific treatment-management frameworks may result in different management pathways and responder classification**




***Note:*** *Simplified representation of key protocol-recommended management differences; full protocols included additional timing, titration, safety, and investigator-discretion considerations.*

[a]Definitions simplified for presentation. PRN active vitamin D and oral calcium allowances differed across endpoint specifications; limited PRN use (≤7 days) was permitted in PaTHway and the CALYPSO EU primary definition, but not in the CALYPSO US and US-reference countries primary definition.

### Implications

- Even when patients are in comparable clinical states, trial-specific treatment-management frameworks could result in different treatment-management decisions.
- As these frameworks are repeatedly applied throughout follow-up, differences in management could accumulate, resulting in increasingly divergent patient-level treatment trajectories.
- Because several composite-response components depended on treatment-management decisions, responder classification was inherently linked to the management framework under which treatment was delivered.
- The direction and magnitude of any resulting impact on comparative treatment effects could not be determined from the available evidence.

## Key takeaway

ITC feasibility requires consideration of how treatment is managed between baseline and outcome assessment, not only whether trials share similar populations, comparators, and endpoint definitions.

### Limitations

- This was a qualitative assessment; the magnitude of the impact of the identified treatment-management differences on response achievement could not be quantified from the available evidence.

**References**

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Poster

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