Collaborate to innovate: iptacopan and RWE in PNH treatment

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NOVARTIS

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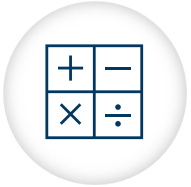
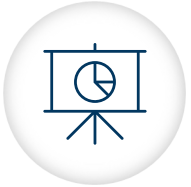
Background

Study design



Methods



Key results

Discussion

Paroxysmal nocturnal hemoglubinuria: iptacopan and integrating RWE

Rare acquired disease characterized by hemolytic-related symptoms[1]

C5 Inhibitors: Eculizumab and ravulizumab prevent IVH[2,3], but many patients remain anemic or transfusion-dependent.[4-6]

Iptacopan Factor B inhibitor (Fabhalta®)

- **APPOINT-PNH**: Demonstrated significant Hb improvements without RBCTs in single arm trial (NCT04820530)[7]
- **APPLY-PNH**: Iptacopan monotherapy showed superior efficacy to C5i in anemic PNH patients on stable C5i regimens (NCT04558918)[7]

despite, no data comparing hematological response of iptacopan with C5i in complement inhibitor-naïve PNH patients are available.

Study Aim: What would have happened to APPOINT-PNH patients had they received anti-C5 instead of iptacopan?

[1]Brodsky, Blood 2014, [2]Hillmen et al. N Engl J Med 2006, [3]Lee et al. Blood 2019, [4]Fishman et al. Hematol Rep 2023, [5]Debureaux et al. Bone Marrow Transplant 2021, [6]Schrezenmeier et al. Ther Adv Hematol 2020, [7]Peffault de Latour et al. N Engl J Med 2024

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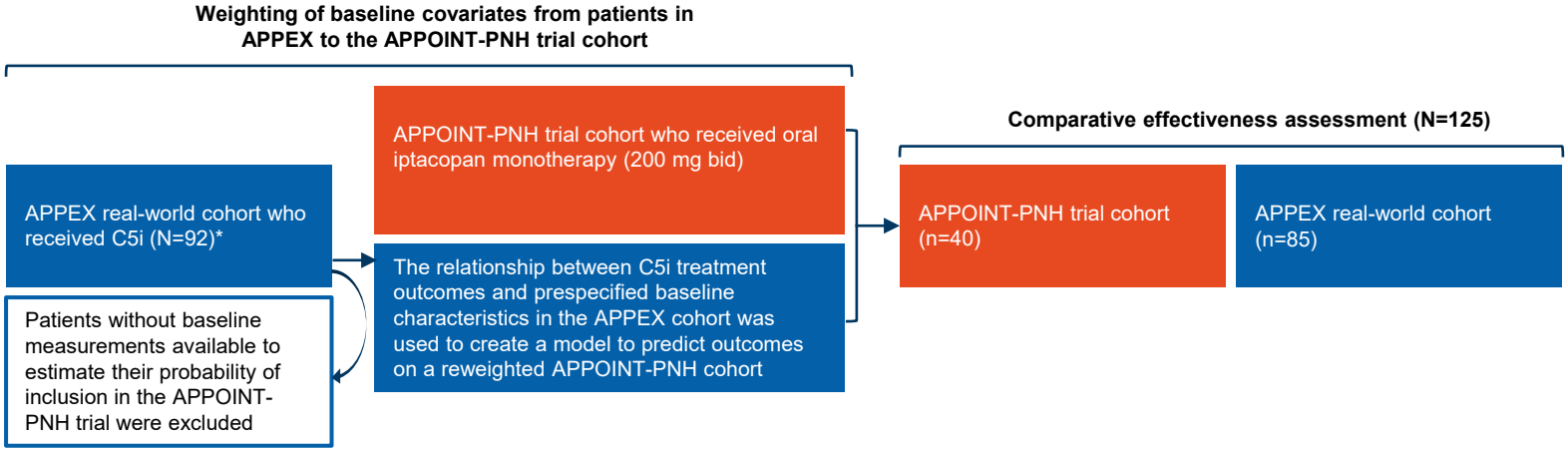
APPEX is a research collaboration retrospective non-interventional study

- This study included patients in APPOINT-PNH who received oral iptacopan monotherapy and the real-world APPEX cohort who received routine C5i treatment at PNH reference hospitals in France and the UK (NCT05842486).



Study design

*Patients received routine C5i treatment at PNH reference hospitals in France and the United Kingdom ; All patients received eculizumab during the treatment period used in this analysis apart from one, who received ravulizumab. bid, twice daily; C5i, C5 inhibitor; PNH, paroxysmal nocturnal hemoglobinuria.

Target trial emulation to mitigate bias through design

- Analyses were adjusted for confounding using a propensity score (PS) and outcome model to construct a weighted prediction of treatment outcomes that would have been observed had APPOINT-PNH participants received C5i instead of iptacopan.
  - PS models probability of receiving treatment with iptacopan in the APPOINT trial.[8]
  - The outcome model is fit on the APPEX cohort and includes covariates identified as **confounders**. The model is then used to predict outcomes in APPOINT-PNH cohort.
- Casual inference methodology:
  - C5i -**bench marking** (indirect comparison)
  - C5i vs iptacopan -**comparative effectiveness** (direct comparison)

[8]Mercatanti, Ann Applied Stat 2014

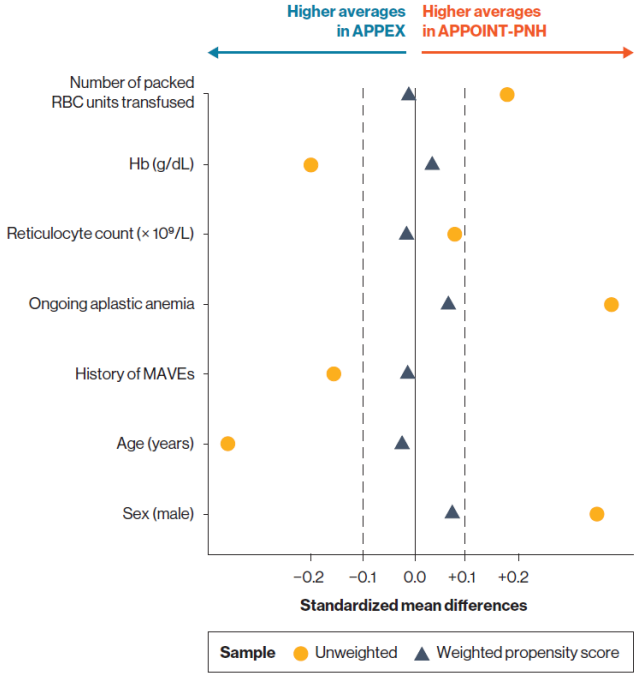
Estimating average Tx effect reflecting APPOINT trial population

- Effectiveness of hematological response was defined as:
  - Proportion of patients who would have achieved an increase from baseline in Hb ≥2 g/dL* in absence of RBCTs;
  - Proportion of patients who would have achieved Hb levels ≥12 g/dL* in absence of RBCTs;
  - Proportion of patients who would have achieved transfusion avoidance;
  - Percentage change from baseline in LDH levels;
  - Change from baseline in reticulocyte count.
- Estimated differences between treatments were derived using orthogonalized score form of the efficient influence function and cross-fitting.[9,10]
- Confidence bounds for differences accounting for multiple imputations in APPOINT-PNH were obtained using Rubin's combination rules.[9,10]

[9]Chernozhukov et al. J Econom 2018, [10]Bach et al. J Star Softw 2024

Derived propensity score weights achieved balance between APPEX and APPOINT

- Plot displaying balance in baseline covariates between APPEX and APPOINT-PNH before and after weighting.
- Age and sex were added to the confounder list representing the impact of unobserved confounding to improve overlap between the two cohorts.



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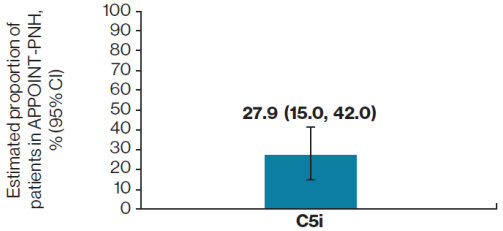
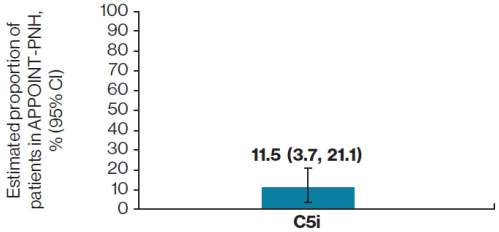
Estimated effectiveness of C5i on hematological response in the APPOINT-PNH trial cohort



A. Hb increase of ≥2 g/dL from baseline in the absence of RBCTs

Estimated proportion of patients in APPOINT-PNH after receiving iptacopan: **92.2%** **(95% CI 82.5, 100.0)**

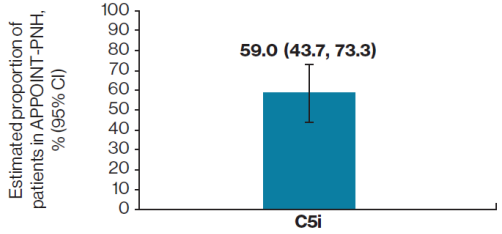


B. Hb level ≥12 g/dL level in the absence of RBCTs

Estimated proportion of patients in APPOINT-PNH after receiving iptacopan: **62.8%** **(95% CI 47.5, 77.5)**

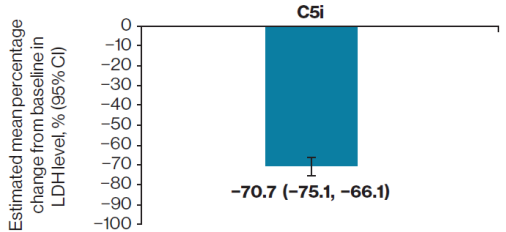
Estimated effectiveness of C5i for hematological response in the APPOINT-PNH trial cohort

C5i, C5 inhibitor; CI, confidence interval; Hb, hemoglobin; LDH, lactate dehydrogenase; RBCT, red blood cell transfusion.



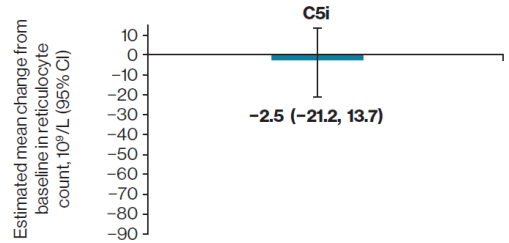
C. Transfusion avoidance

Estimated proportion of patients in APPOINT-PNH after receiving iptacopan: **97.6%** **(95% CI 92.5, 100.0)**



D. Percentage change from baseline in LDH levels

Adjusted mean percentage change from baseline in LDH levels in APPOINT-PNH after receiving iptacopan: **−83.6%** **(95% CI −84.9, −82.1)**



E. Change from baseline in reticulocyte count

Estimated mean change from baseline in reticulocyte count in APPOINT-PNH after receiving iptacopan: **−82.5 × 10⁹/L** **(95% CI −89.3, −75.6)**

Holt et al (2024), P074 EBMT 50th annual meeting

Comparative effectiveness of iptacopan and C5i for hematological endpoints in APPOINT-PNH

- The APPEX cohort was used to learn the effect of C5i on hematological response endpoints in complement inhibitor-naïve patients with PNH.
- The differences in treatment effect between iptacopan in patients from APPOINT-PNH and C5i in patients from APPOINT-PNH had they received C5i, learned from the APPEX response data, are shown below.
- The results favored iptacopan over C5i for all hematological endpoints analyzed.

Endpoint	Estimate	Difference in treatment effect (iptacopan vs C5i)
Response as a ≥2 g/dL increase in Hb from baseline in the absence of RBCTs	Difference in proportions, % (95% CI)*	68.2 (40.9, 95.6)†
Response as having Hb level ≥12 g/dL in the absence of RBCTs	Difference in proportions, % (95% CI)*	53.4 (31.4, 75.3)†
Transfusion avoidance	Difference in proportions, % (95% CI)*	38.8 (15.1, 62.5)†
Percentage change from baseline in LDH levels	Ratio of geometric means (95% CI)*	0.51 (0.40, 0.67)†
Change from baseline in reticulocyte count	Difference in change from baseline, 109/L (95% CI)*	−75.5 (−106.9, −44.2)†

*Derived using the orthogonalized score form of the efficient influence function and cross-fitting; †In favor of iptacopan.
C5i, C5 inhibitor; CI, confidence interval; Hb, hemoglobin; LDH, lactate dehydrogenase; RBCT, red blood cell transfusion.

Discussion

APPEX results	CI-naïve patients with PNH may experience greater improvements with iptacopan vs C5i, consistent with efficacy of C5i in clinical trials.[2,3]
Collaboration	Several pillars of analytics and beyond Novartis
Transforming RWD to RWE	Visit frequency in APPEX according to clinical practice. Statistical methods used to manage missing or incomplete data.
Generalizability	APPEX study could not balance for regional differences. However, no differences in efficacy expected.[11-13]
Impact	Health Authority and HTA submissions

[2]Hillmen et al. N Engl J Med 2006, [3]Lee et al. Blood 2019, [11]EMA. Soliris (eculizumab), [12]EMA. Ultomiris (ravulizumab), [13]FDA. FABHALTA® (iptacopan)

Q&A

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