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Virtual Patient Cohorts using Modeling and Simulation to Support Drug Development in Rare Diseases

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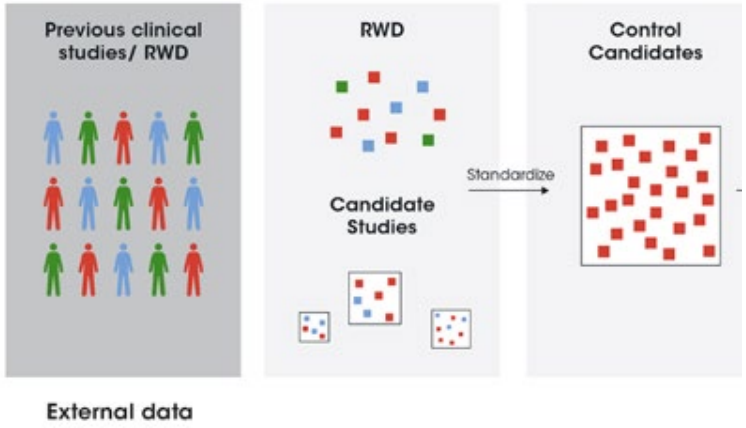
Summary

- Increased need for tools to boost **drug development and adoption** in rare diseases is acknowledged by regulators
- Novartis is dedicated to develop sound approaches to support this effort, PMX group has been actively involved in various Consortia
- For rare diseases, developing methodologies to contextualize the readouts of single arm trials is very challenging also due to small sample size
- We present how PKPD models can be used to generate **“virtual” control patients** on example of iptacopan in Paroxysmal Nocturnal Hemoglobinuria to support **drug approval** and **potential post-approval clinical adoption**

Rare diseases: large, heterogeneous, underserved patient community

- Affect ~350 million people worldwide (about 4% of entire population), 50% are children
- Only 5% of diseases have approved treatments
- High societal and economic burden
- Urgent need for better ways to diagnose and to treat their disease
- Single arm trials ➔
  - No direct comparison with placebo or an active control
  - **Protracted drug approval cycle**
  - **Limited clinical adoption** of new therapies

Standard approach: Synthetic Control Arm



RWD: Real-world data (e.g., disease registries)

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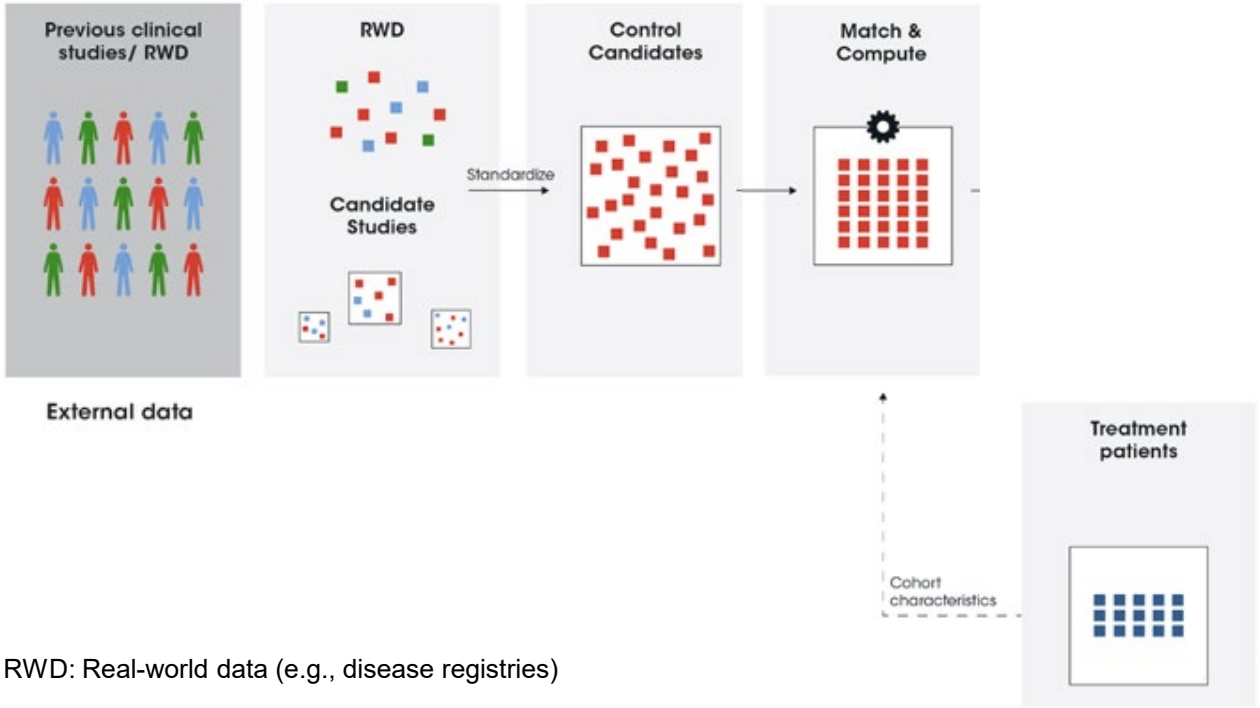

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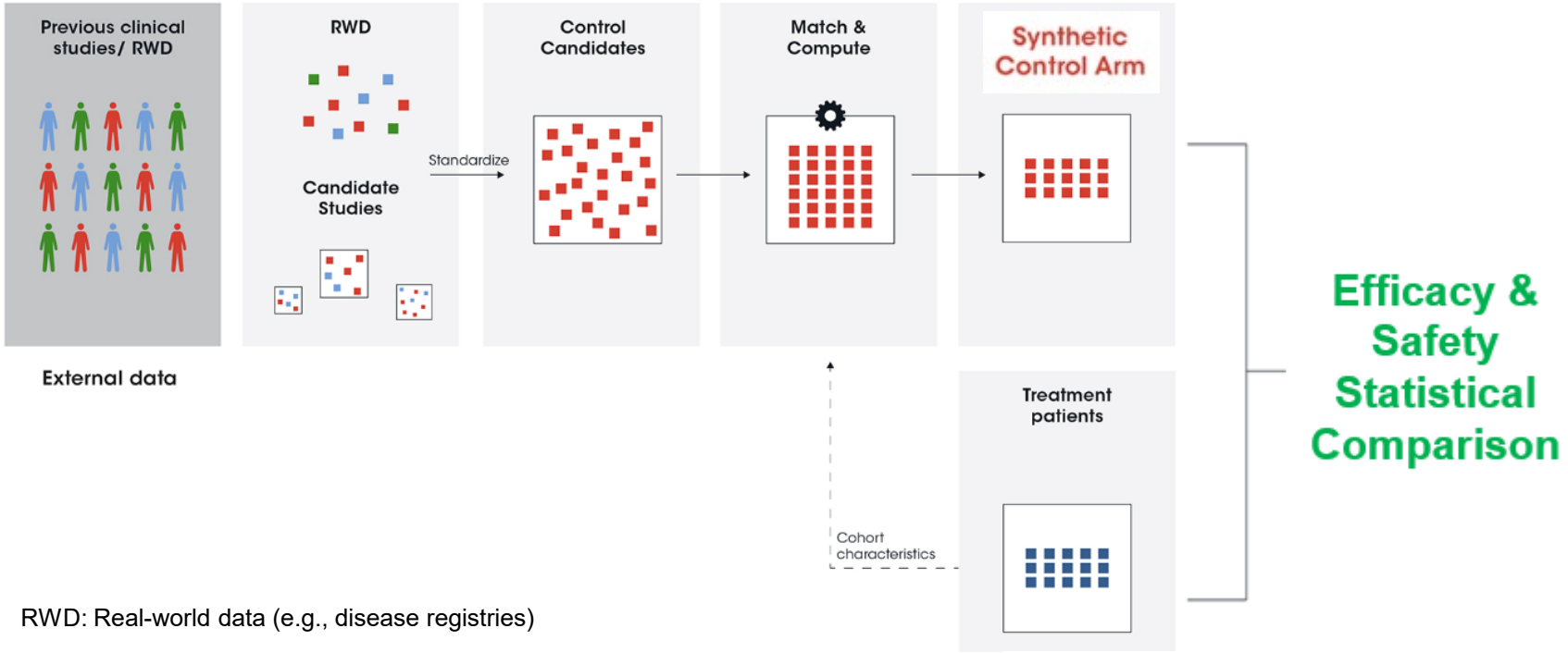

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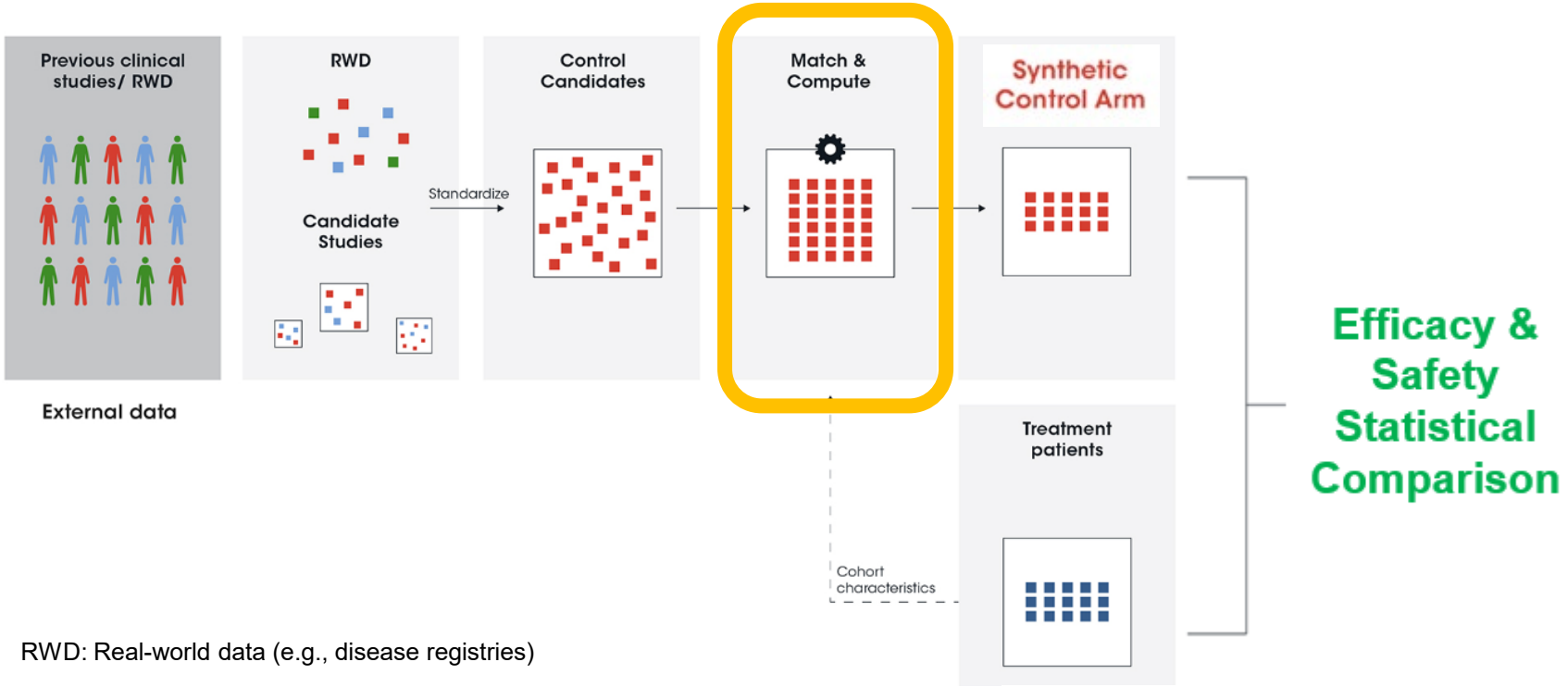
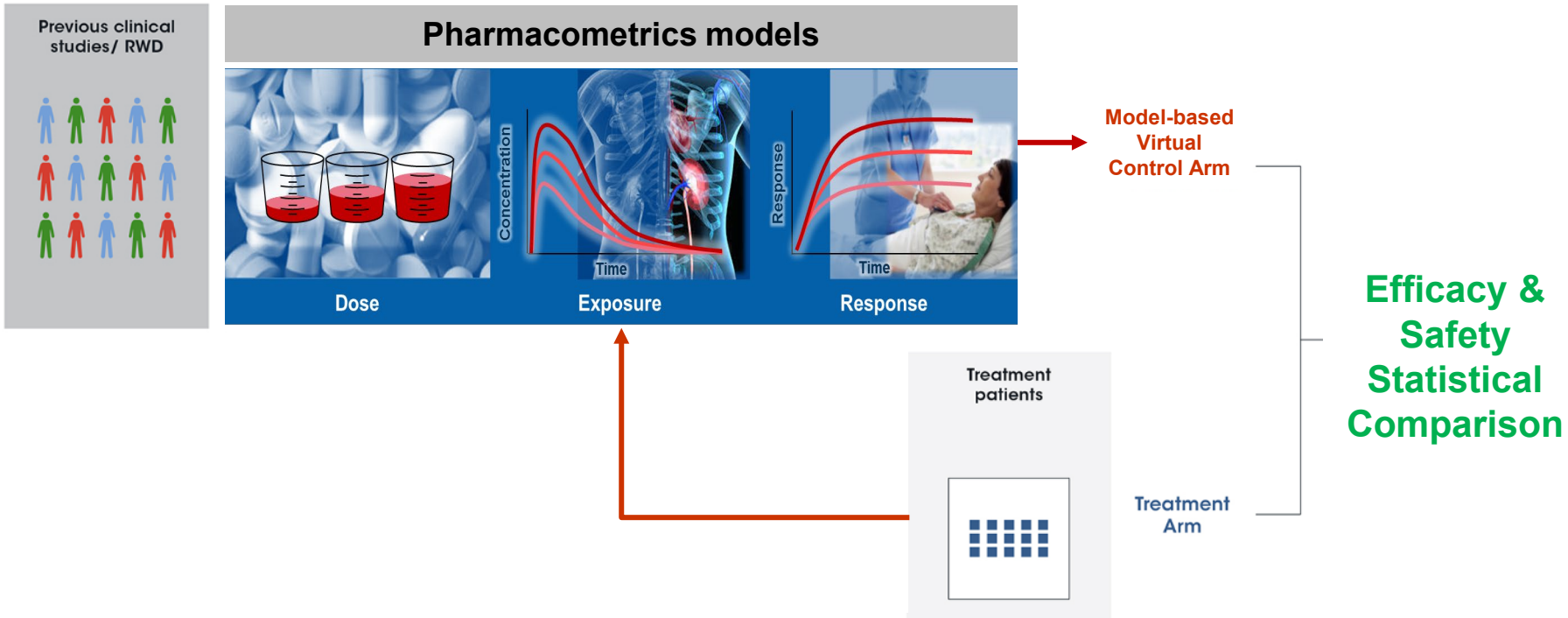
Synthetic Control Arm: several salient limitations



RWD: Real-world data (e.g., disease registries)

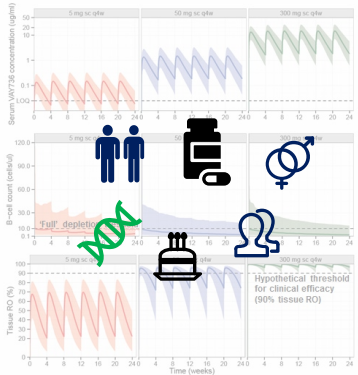
Our objective: generate ‘Virtual Patients’ using PMX modeling



Advantages of model-based Virtual Arm

How does it work?

Fit model



What happens if?

Simulate

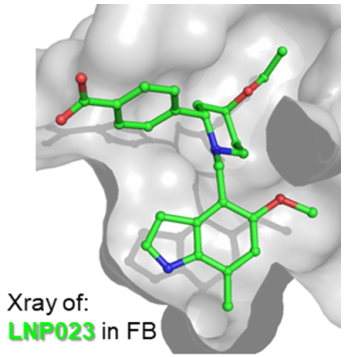
- **Disease and response dynamics** vs. cross-sectional clinical endpoint evaluation
- **All data** vs. selected sample
- **Account for confounders, reduce bias**
- **Imputation of missing data** from the model
- **Scenario evaluation**

Case study: iptacopan

Pipeline in a pill

Iptacopan/LNP023

- Iptacopan, an oral, selective and potent first-in-class **factor B inhibitor** targeting the alternative complement pathway and acting upstream of C5



Paroxysmal nocturnal Hemoglobinuria (PNH)

- Genetic (somatic) mutation in HSCs; resulting in red blood cell hemolysis & thrombosis (potentially life-threatening)
- Rare disease: US incidence ~1.3/million
- **Standard-of-care (SoC) is anti-C5 therapy (high treatment burden)**
- **Over 80% of patients suffer anemia** (Hb < 10 g/dL) and many remain transfusion-dependent despite anti-C5 therapy [3]

Hemolytic Erythrocyte with complement MAC

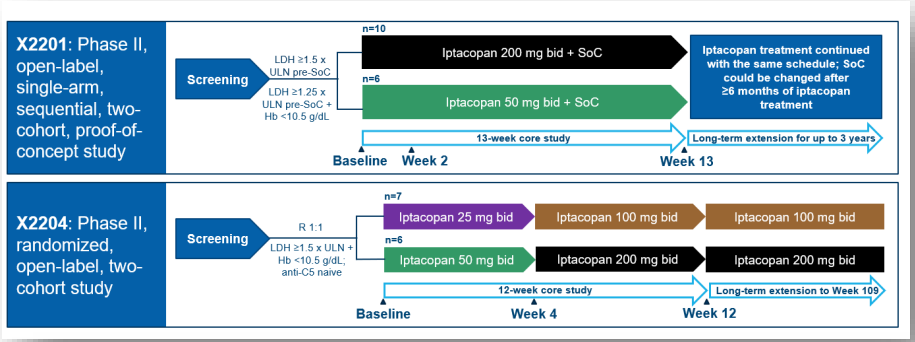
Other indications

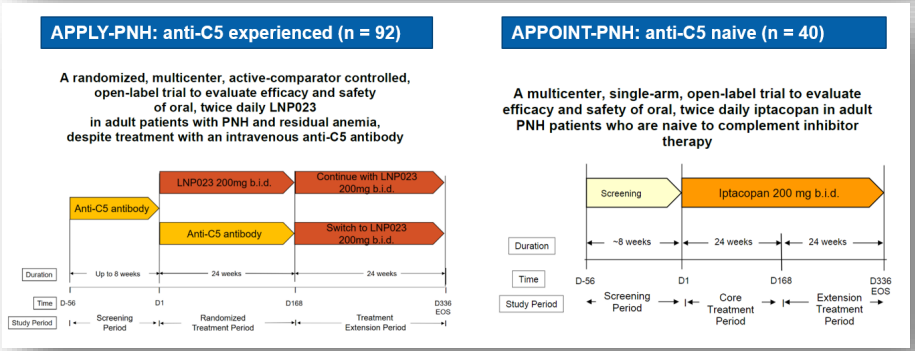
- IgAN (renal)
- C3G (renal)
- IC-MPGN (renal)
- aHUS (hematology)
- Etc.

Development program of iptacopan in PNH

- Two Phase 2 trials
  - X2201: Iptacopan 200 mg bid as add-on to anti-C5 treatment [4] (NCT03439839)
  - X2204: Iptacopan as monotherapy in treatment-naive patients [5] (NCT03896152)

- Two Phase 3 trials
  - APPLY-PNH: iptacopan 200 mg bid vs anti-C5 in treatment-experienced patients (NCT04558918)
  - APPOINT-PNH: iptacopan 200 mg bid in treatment-naive patients, open label **single arm** (*NCT04820530*)





PKPD modeling for iptacopan in PNH

- Longitudinal modeling of Hb data (4 PNH studies of iptacopan, n=161)
- Model adequately characterized one of the components of the primary endpoint, haemoglobin (Hb) response
- Was used to rationalize the registered dose (200 mg bid) in the submission dossier

Iptacopan PKPD model for Hb

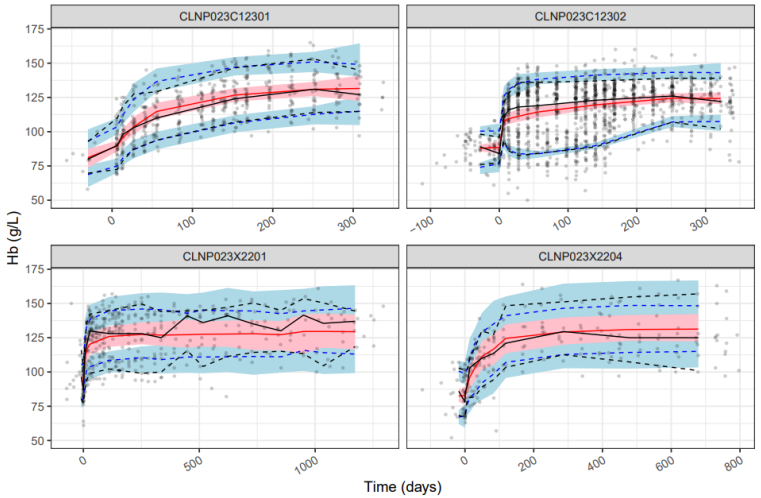
$$\frac{dY(t)}{dt} = k_{in} - k_{out}(t)Y(t), \text{ where}$$

$$k_{out}(t) = \frac{k_{in}}{Y_{base}}\left(1 - \left(\frac{Y_{TRT} - Y_{base}}{Y_{TRT}}\right)S(t)\right)$$

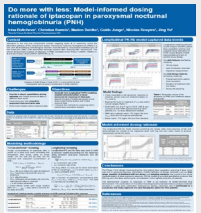
$$S(t) = \left(\frac{C^{\gamma}(t)}{EC_{50}{}^{\gamma} + C^{\gamma}(t)}\right)$$

At steady state, $Y_{SS} = Y_{Base} + (Y_{TRT} - Y_{Base})\left(\frac{C_{SS}^{\gamma}}{EC_{50}{}^{\gamma} + C_{SS}^{\gamma}}\right)$

- $Y(0) = Y_{Base}$: Hb level before the start of treatment
- Y_{TRT}: maximally improved Hb level on treatment
- k_{in}: production rate of red blood cells (RBCs)
- k_{out}: turnover rate of RBCs
- $S(t)$: drug effect function inhibits elimination
- EC_{50}: iptacopan concentration at which the half-maximal effect is reached



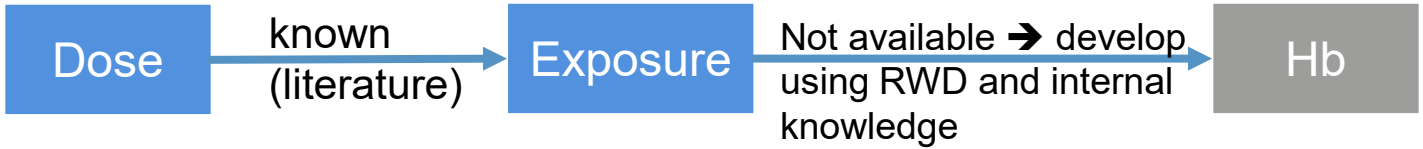
➢ For more details on the PK-Hb modeling, visit poster I-020



Leveraging internal data and SoC from real world data (RWD)

Iptacopan

Eculizumab



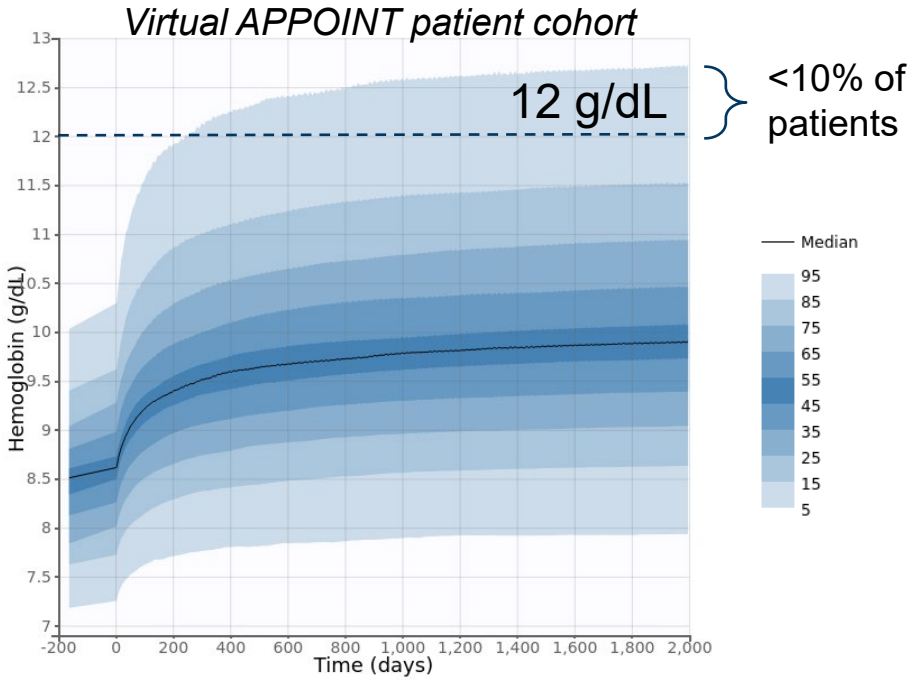
Exposure-response model for Hb using internal/ external knowledge

- SoC: anti-C5 mAbs **eculizumab**/ravulizumab
- PKPD model for Hb using published literature data:
  - 1-cpt PK model with CL and V values fixed to values from literature [1, 3]
  - Indirect response model for Hb:
    - Kin fixed to a value from our internal model for iptacopan
    - Emax and EC50 values derived from RWD

Virtual Patient Cohort generation

Simulation of Hb response under SoC

- Simulate the Hb response of patients as in iptacopan APPOINT-PNH single-arm trial (n=40, adjusted for sex and baseline Hb), but as if they were treated with SoC (eculizumab)
- **Eculizumab dosing** as per label
- **APPOINT-PNH** readout: iptacopan achieved **Hb levels of at least 12 g/dL** without the need for red blood cell (RBC) transfusions in **62.8%** (95% CI, 47.5%-77.5%) of patients
- Simulation results generate evidence of **better anemia control under iptacopan** as compared to SoC and hence allow to contextualize the results of APPOINT



INVENTS Consortium

Innovative designs, extrapolation, simulation methods and evidence-tools for **rare diseases** addressing regulatory needs https://ecrin.org/projects/invents

- **Funding:** Horizon Europe (N 101136365)
- **Budget:** €6M
- **Coordinator:** INSERM
- **Duration:** 5 years (Jan 2024 - Dec 2029)
- **Overall objective**: To provide clinical trial stakeholders, trialists and regulators with a generalizable framework encompassing methods, workflows and evidence-tools to improve the level of evidence in regulatory decision making in rare diseases.
- **Framework** to be used to make the most of sparse evidence, to synthesize (seemingly) disparate data, and to robustly bridge between more or less well-understood indications

Conclusions

- Modeling and Simulation techniques using Clinical Trial Data complemented with RWD allow to generate **Virtual Patient Cohorts** and to substitute SoC information missing in single arm trials
- Major advantages over other techniques are:
  - Allow for **indirect comparison** while **accounting for confounders** (differences in MoA, trial design and populations btw. clinical trial and RWD) inference in the situations where data is sparse
  - Allow for knowledge leveraging between **clinical trial** and **RWD**
  - Allow for **scenario evaluation** beyond those observed to address questions of interest to a clinician, regulator, or payer
- Joint work with Regulatory Agencies, HTA bodies, Academia and Pharma will further **enhance the acceptance of Virtual Patient Cohorts as a tool for drug approval and post-approval adoption**

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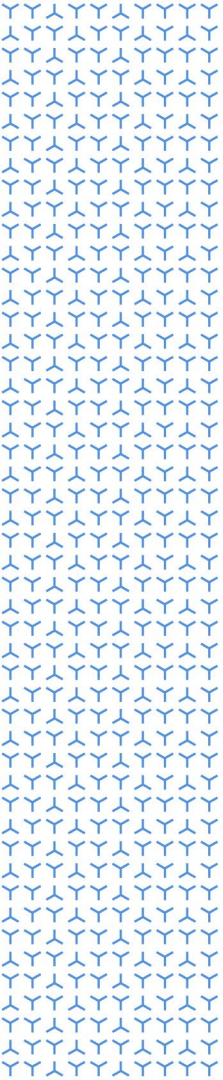
- INVENTS Consortium



Thank you

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