Implementation of an MIDD strategy for ruxolitinib dosing in pediatric populations, and varying opinions of regulators

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Background and rationale for an MIDD strategy in ruxolitinib dosing in pediatrics

Ruxolitinib (Jakavi®) is a potent, reversible, and selective **Janus Kinase (JAK) 1 and JAK2 inhibitor** approved globally for treatment of adults with MF/PV, and patients > 12 years old with Graft vs. Host Disease (GvHD).

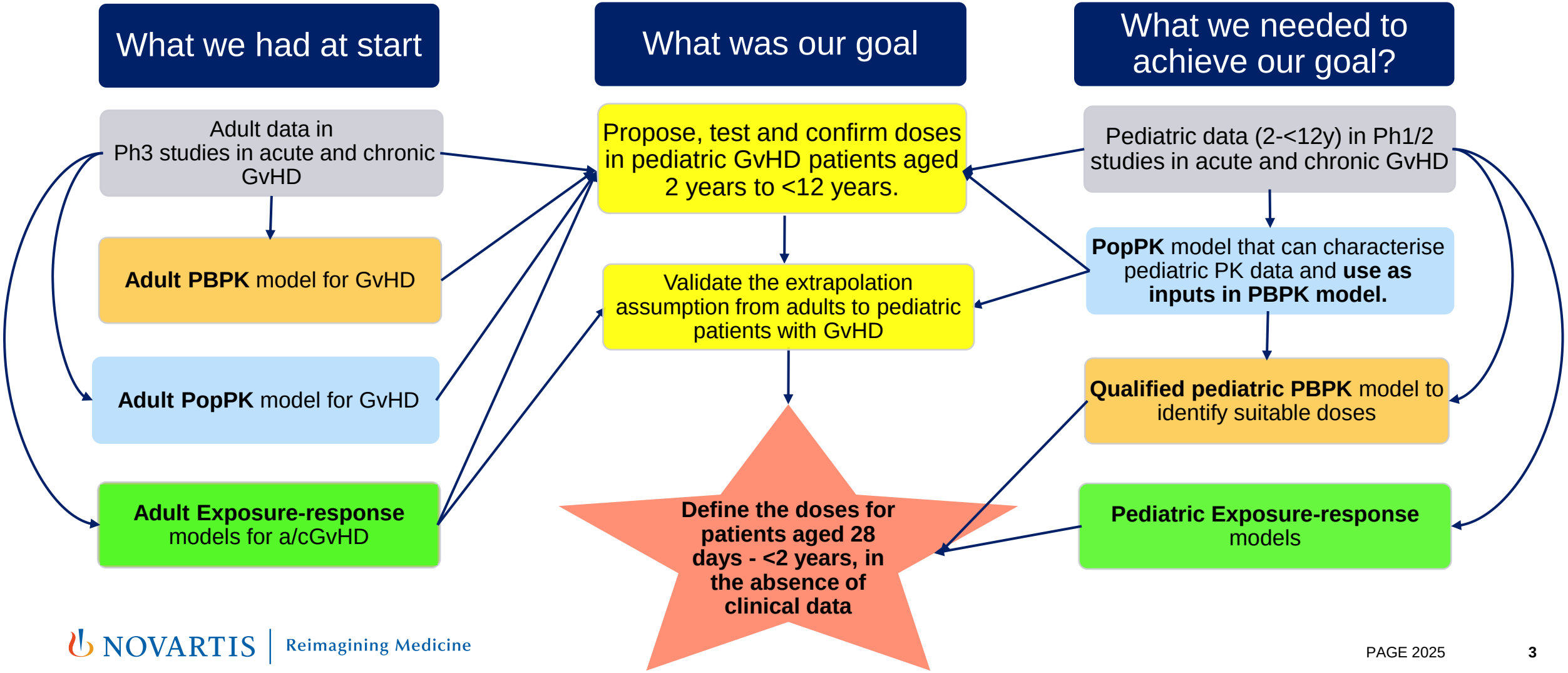
Given the amount of information on ruxolitinib in various indications, a **Model Informed Drug Development (MIDD) strategy** was agreed with EMA's PDCO and other Health Authorities to identify the dose in pediatric GvHD patients < 12 years old.

An exposure matching concept was implemented based on the principle of similarity in disease and PK between adults and pediatrics. To implement this strategy, multiple modeling techniques were applied:

- **Physiologically Based PK (PBPK) modeling was used for:**
  - **Starting dose recommendation in GvHD patients aged 2<12y:** targeting the efficacious adult AUC associated with the approved dose (10 mg BID)
  - **Extrapolation to patients <2y:** targeting the AUC observed in older pediatric patients.
- **Population PK (PopPK) and Exposure-Response (ER) models** were used for:
  - **Dose confirmation in patients aged 2-<12y:** validating the exposure-matching concept

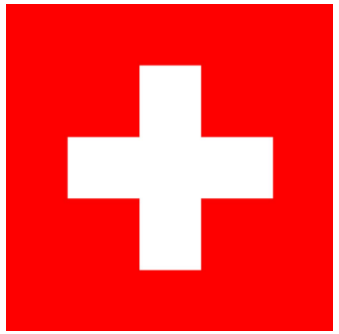
MF, myelofibrosis: PV, Polycythemia Vera

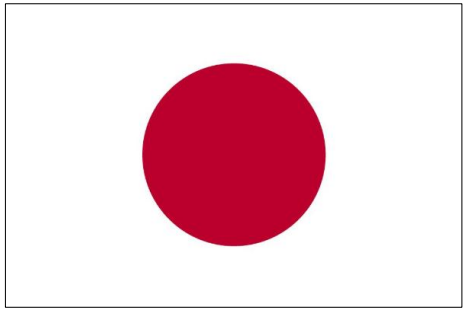
MIDD strategy:
Adult GvHD data + multiple modeling techniques → dose to be tested for 2-<12y
Pediatric (2-<12y) data + updated models → dose predictions for <2y



Doses submitted in EU, Switzerland, Japan (and more)

GvHD	Doses	Note
Adolescent ≥ 12 years	10 mg BID	Already Approved w. adults
Pediatric ≥ 6 years, < 12 years	5 mg BID	Tested
Pediatric ≥ 2 years, < 6 years	4 mg/m^2 BID	Tested
Pediatric ≥ 28 days, < 2 years	4 mg/m^2 BID	No patients enrolled in clinical trials





Dose recommendation & confirmation in a/cGvHD patients aged 2-<12y

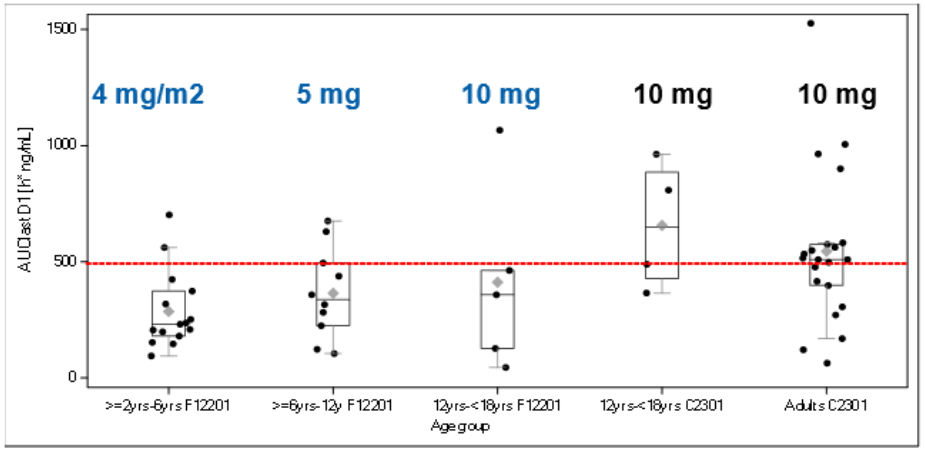
Pediatric ≥ 6 years, < 12 years	5 mg BID
Pediatric ≥ 2 years, < 6 years	4 mg/m^2 BID

Dose recommendations for patients aged 2-<12 years was informed by PBPK modeling

Predicted exposures to match the median AUC observed in adult aGvHD patients

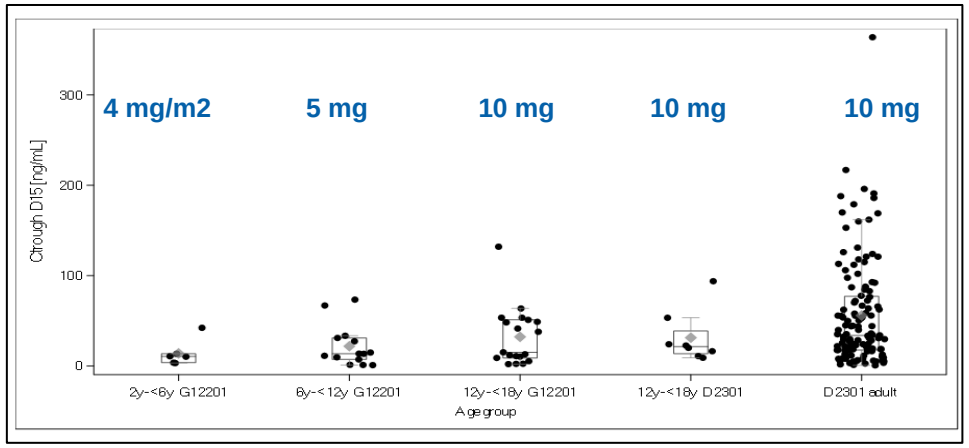
- PBPK model developed in healthy volunteer adults
  - Utilised DDI data to capture fraction metabolized by CYP3A4 and CYP2C9
- PBPK model adapted to match the PK profiles in aGvHD adult patients (10 mg BID)
- GvHD PBPK model was used to predict pediatric (2-<12y) exposure in a/cGvHD

aGvHD



Overlap of observed AUC ranges deemed sufficient for exposure matching and dose confirmation, given small sample size

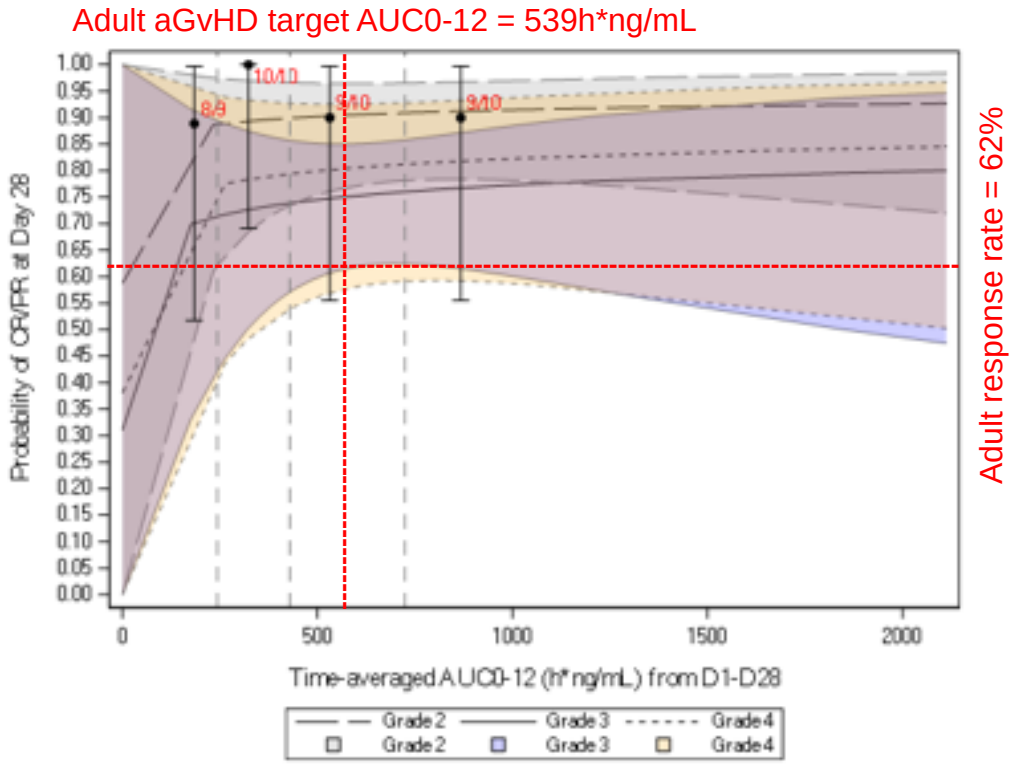
cGvHD



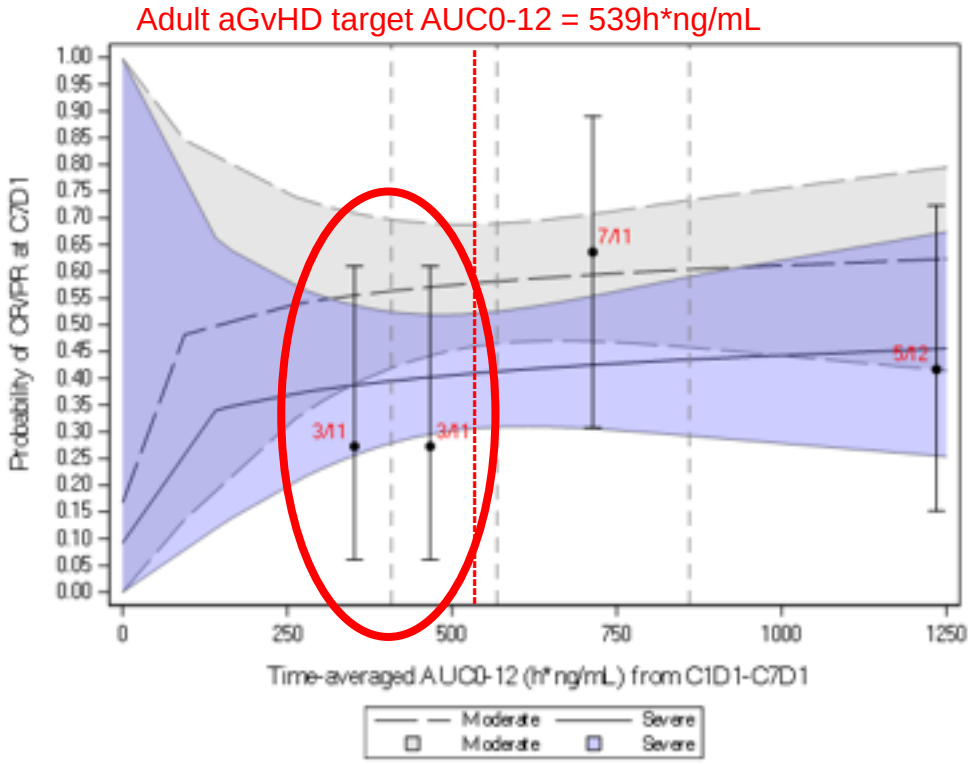
Low exposures observed, particularly for younger patients, at later time points, but still within the range of adult data, supporting the exposure matching assumption

Doses confirmed in aGvHD pediatric (2-<12y) patients, and subsequently cGvHD pediatric patients

aGvHD



cGvHD



Good efficacy was observed for all patients, comparable to the adult efficacy rate, justifying the doses

No formal dose confirmation performed for cGvHD

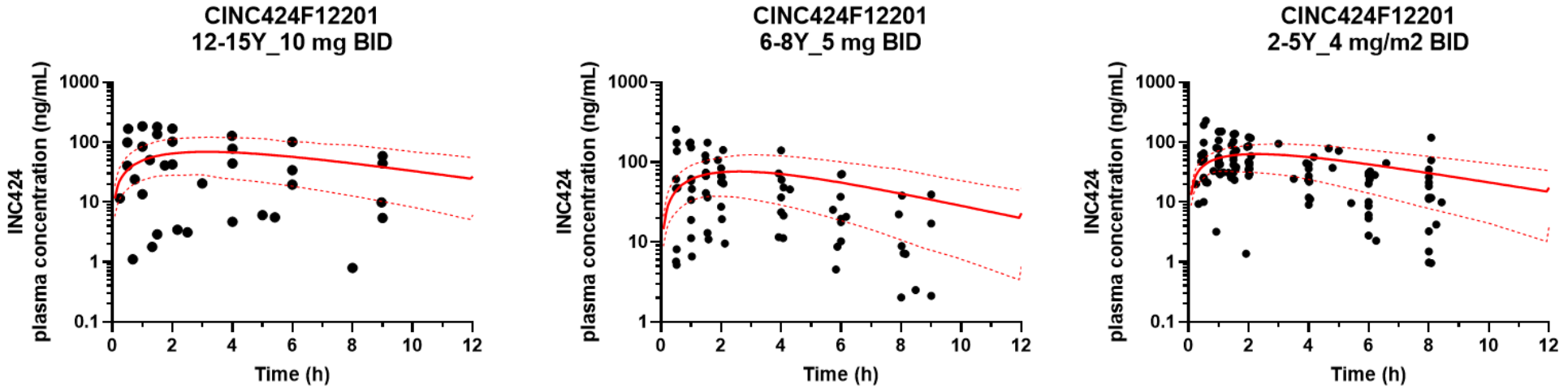
Lower response rates observed at lower exposures, but a generally flat curve and overlapping intervals
→ supporting dose registration

Extrapolation to patients <2y

Pediatric ≥ 28 days, < 2 years	4 mg/m^2 BID

Adult PBPK model was updated with pediatric (2-<18y) data and PopPK results, for dose prediction in patients <2y

- Anatomical and physiological age-dependent changes, as well as ontogeny profiles of CYP2C9 and CYP3A4 (main metabolic drivers of ruxolitinib clearance) were incorporated into the GvHD PBPK model to create a pediatric GvHD PBPK model

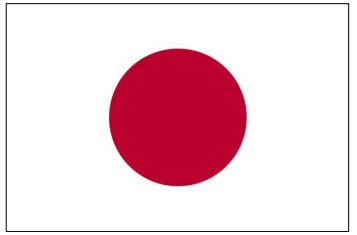


- Some uncertainty was observed, however due to wide therapeutic range of ruxolitinib and acceptable efficacy rates (as seen with ER modeling):
  → **model was considered qualified in this population**

Exposures were predicted in patients aged <2y and dose (4mg/m^2) identified to match the median exposure in older pediatric patients.

Submitted doses and regulatory feedback

First approval in the world, for Japan



Novartis initially proposed

Indications	6-12 years (tested)	2-6 years (tested)	28 days-2 years
aGvHD	5 mg BID	4 mg/m^2 BID	4 mg/m^2 BID
cGvHD	5 mg BID	4 mg/m^2 BID	4 mg/m^2 BID

PMDA approved as submitted for aGvHD and cGvHD for patients >0 years old (not limited to 28 days)

SR, steroid-refractory

EMA - Interactions with CHMP

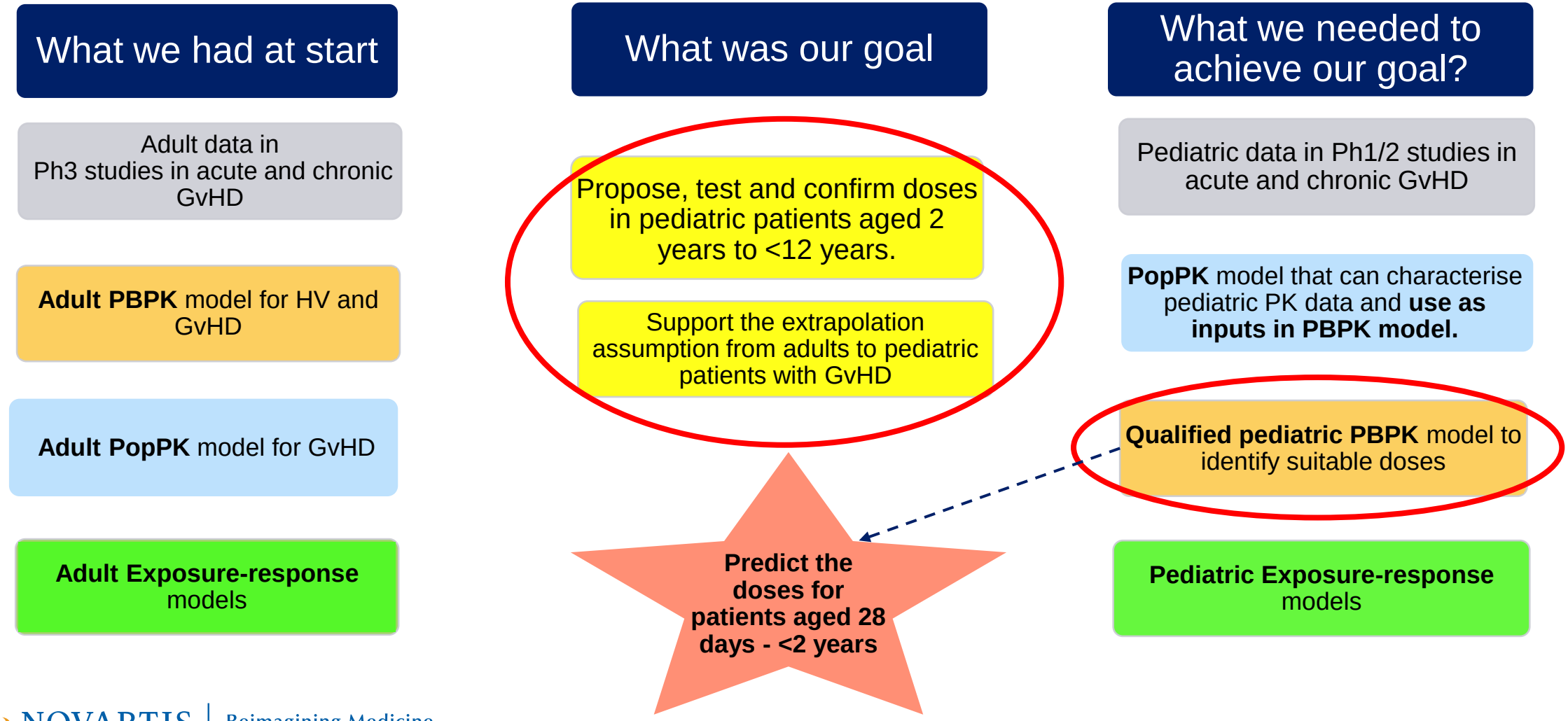
Several major objections

- PK bridge using PopPK predicted time-averaged AUC *vs.* a target reference **value** (median) in adults is not adequate
  - **<u>Recommendation</u>**: bridge using **observed** PK data on **Day 1** (prior to any dose modifications having been made) and compare to **adult reference range** (rather than a specific value) to confirm extrapolation of efficacy
  - **<u>Request</u>**: Explore additional doses for patients <12y through modeling & simulation
- PBPK model not qualified due to high uncertainty associated with model performance
  - **<u>Recommendation</u>**: Consider ontogeny of main metabolic enzymes (CYP3A4 & CYP2C9) in a PopPK model to predict dose under 2 years
    - *Ruxolitinib clearance defined as a function of time-varying (with age) CYP ontogenies and scaled by the proportion metabolized by each CYP*
  - **<u>Request</u>**: Discuss the uncertainty of the exposure predictions across the age range <2 years as it is perceived that the uncertainty about the PK is higher the younger the patient is

MIDD strategy: Evidence associated with pediatric doses (28d-12y) is inconclusive

Lack of PK Bridge to adults for exposures on Day 1

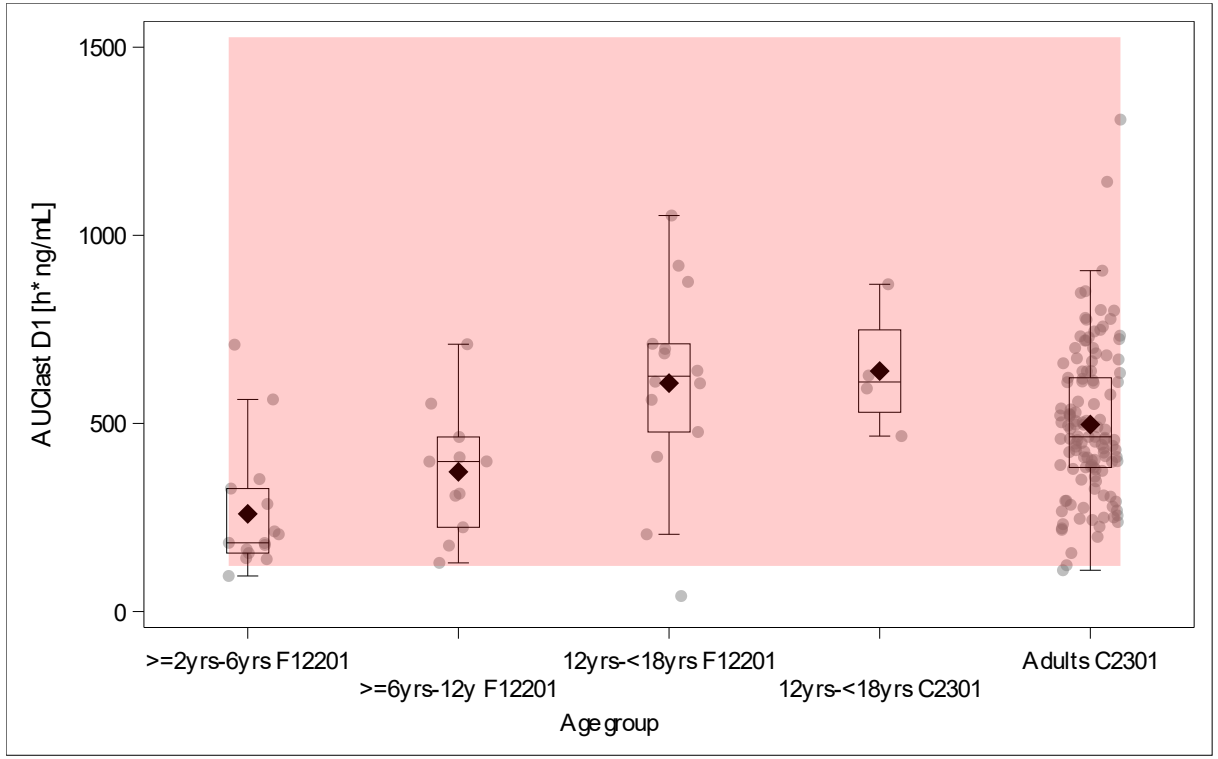
PBPK model considered not qualified



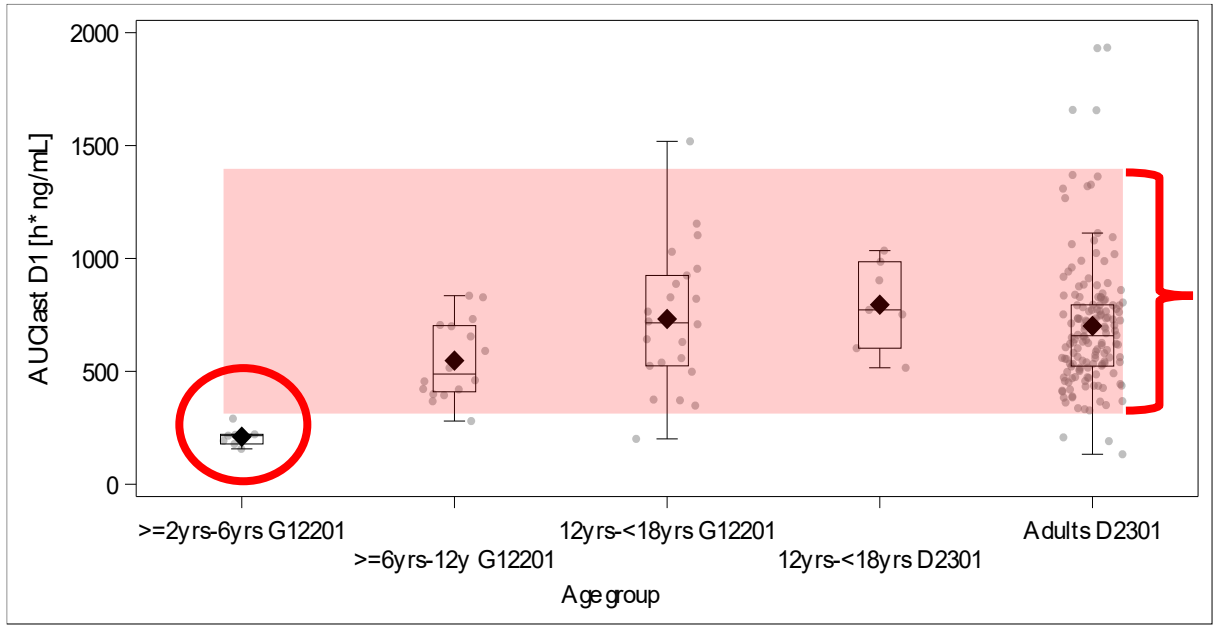
PK Bridge established for aGvHD, and cGvHD >6y

Predicted parameters on Day 1 were within the adult reference range, except for the youngest cGvHD patients

Acute GvHD



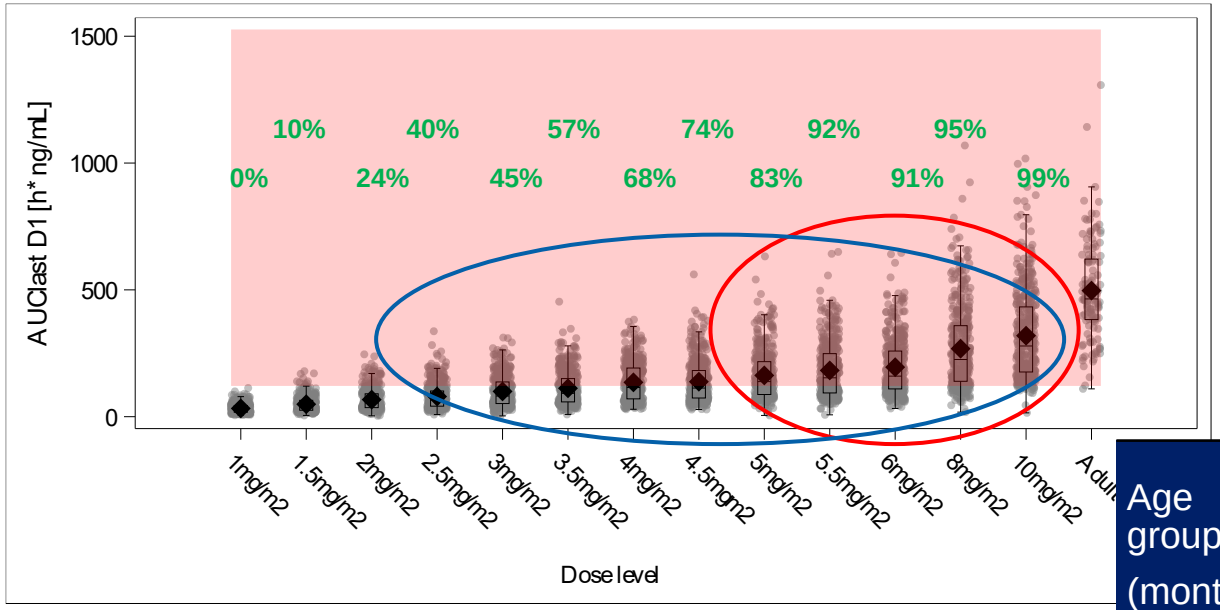
Chronic GvHD



→ reevaluate doses for younger patients based on observed data to bring further into the adult range

Comparability of predictions from the PopPK with ontogeny and PBPK proposed a higher dose to be administered to patients <6y

AUClast: Acute GvHD between 1 to 2 years



red: dose level with highest proportion of PopPK (ontogeny) predictions in reference range
blue: dose proposed by PBPK (to match adult observed reference range)
Green: proportion of AUClst predictions within adult reference range

Comparisons of PopPK and PBPK modeling showed good overlap of proposed doses (except for very young, cGvHD patients)

Chronic GvHD

Age group (months)	Original PBPK dose predictions	**PBPK dose predictions** targeting the 5th-95th percentiles	**Updated PopPK dose predictions** targeting the 5th-95th percentiles
1 to <2	4 mg/m^2	3 – 6 mg/m^2	> 10 mg/m^2
2 to <6	4.5 – 5 mg/m^2	4 – 6 mg/m^2	> 10 mg/m^2

Doses that consistently provided predictions in adult reference range were identified, and 8mg/m^2 selected as optimal, most consistent dose for registration

Second approval in the world, for EU

Novartis initially proposed

Indications	6-12 years (tested)	2-6 years (tested)	28 days-2 years
aGvHD	5 mg BID	4 mg/m^2 BID	4 mg/m^2 BID
cGvHD	5 mg BID	4 mg/m^2 BID	4 mg/m^2 BID

EMA approved

Indications	6-12 years	28d - <6 years
aGvHD	5 mg BID	8 mg/m^2 BID
cGvHD	5 mg BID	8 mg/m^2 BID (patients >6mo.)

SR, steroid-refractory

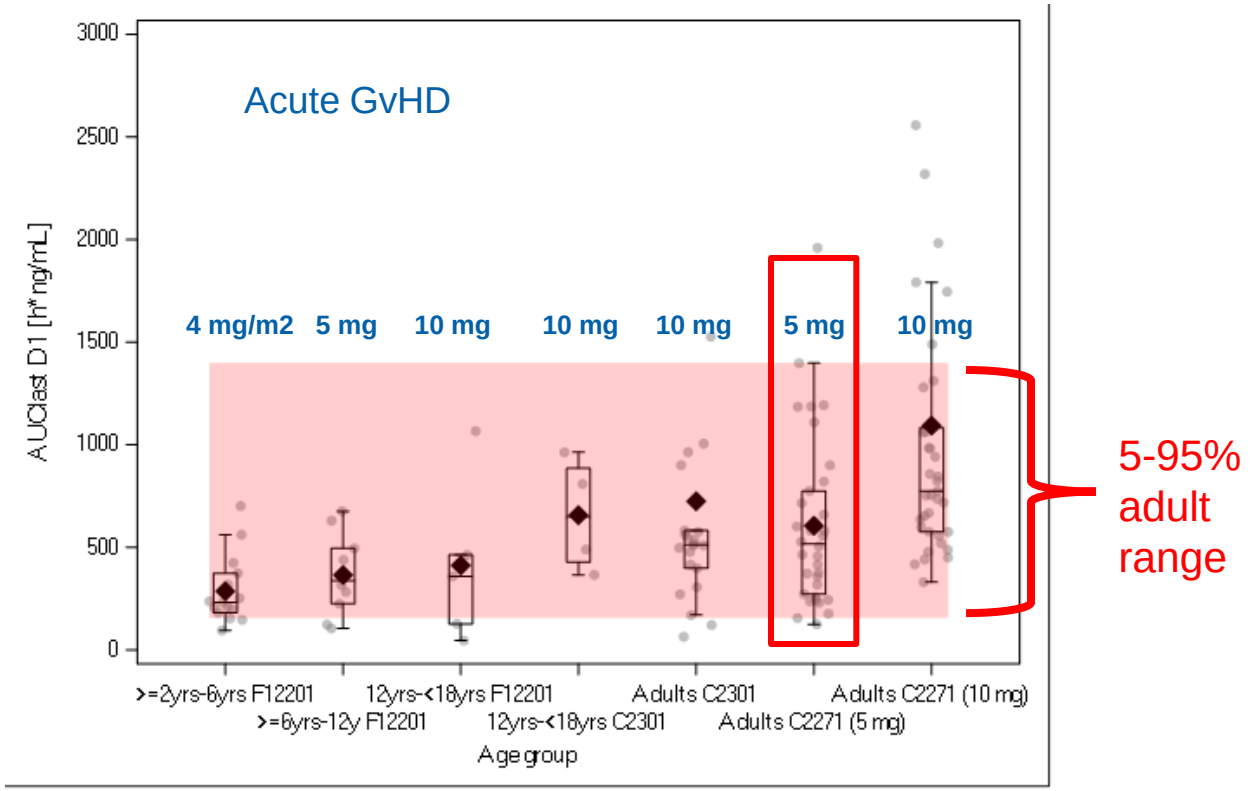
Interactions with Swissmedic

Major objections after seeing EMA responses

- Acute GVHD: PK bridge with the adult dose of 10 mg BID not adequate as starting dose is 5 mg BID in Switzerland
  - **Request**: Compare to the Day 1 exposures associated with 5mg
    → accepted ✓

- PBPK model not qualified
  - ➢ Commented that PopPK approach with ontogeny reasonable but **still no clinical evidence in patients under 2 years old**

PK bridge on Day 1



Limited approval in Switzerland

Novartis initially proposed

Indications	6-12 years	2-6 years	28 days-2 years
aGvHD	5 mg BID	4 mg/m^2 BID	4 mg/m^2 BID
cGvHD	5 mg BID	4 mg/m^2 BID	4 mg/m^2 BID

Swissmedic approved

Indications	6-12 years	2-6 years	28 days-2 years
aGvHD	5 mg BID	4 mg/m^2 BID	Not approved
cGvHD	Not approved	Not approved	Not approved

Differing opinions of regulators on doses proposed by MIDD vs. observed clinical data

- Due to a flat ER curve, and wide therapeutic range of ruxolitinib, **all approved doses are efficacious and safe to administer to pediatric GvHD patients**.
- Constructive feedback from EMA allowed for a **more optimal and safe** regimen to be approved, utilizing multiple complementary modeling techniques to increase confidence.
- Other regions accept the modeling, but believe it is **not sufficient to replace clinical evidence** (data).

→ **When the aim is to reduce burden to pediatric patients (fewer patients, less PK collection, faster access to drugs), how can we improve regulatory acceptance of such approaches in all regions?**

- → Plan to “cross-validate” modeling approaches to increase confidence
- → Reevaluate ALL doses with modeling approaches throughout the pediatric development lifecycle

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Thank you !