Authorised medicines and regulatory considerations by EMA

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The opinions in this presentation are personal, and should not be interpreted to represent the view of the Finnish Medicines Agency, CHMP/SAWP or EMA

Overview of the approved products : SCD

Invented name /EPAR link	INN	Outcome	Type of approval	Indication wording (abbreviated)	Outcome date
Siklos	hydroxycarbamide	positive	Full MA	Prevention of recurrent painful vaso-occlusive crises	26/04/2007
	hydroxycarbamide	negative	N/A	Treatment of severe chronic anemia	22/07/2021
Xyndari	glutamine	withdrawn	N/A	Treatment of sickle cell disease (SCD)	29/05/2019
Xromi	hydroxycarbamide	positive	Full MA	Prevention of vaso-occlusive complications	12/10/2020
Xromi	hydroxycarbamide	positive	Full MA	Prevention of vaso-occlusive complications (over 9 months of age)	22/02/2024
Adakveo	crizanlizumab	positive	Conditional approval	Prevention of recurrent vaso occlusive crises The marketing authorisation for Adakveo has been revoked by the European Commission on 03/08/2023 .	25/02/2021
Oxbryta	voxelotor	positive	Full MA	Treatment of haemolytic anaemia	16/12/2021
Casgevy	exagamglogene autotemcel	positive	Conditional approval	Treatment of severe sickle cell disease (SCD)	14/12/2023

Xyndari and Adakveo – why the data was not sufficient?

Xyndari (glutamine) – withdrawn during the assessment process

"The main study did not show that Xyndari was effective at reducing the number of sickle cell crises or hospital visits".
VOC rate 3.54 vs. 3.97 for glutamine vs. placebo, rate ratio 0.89, 95.5%CI: 0.75, 1.06), p = 0.193, issues with early drop-out, handling of missing data, concomitant medications.

Adakveo (crizanlizumab) – conditional approval revoked in Art 20 process

CMA: median of 1.63 VOCs in the 5 mg/kg crizanlizumab group compared with 2.98 VOCs in the placebo group, -1.01 (95% CI [-2.00, 0.00]), p=0.010
Uncertainties on magnitude of effect, differences of product versions during development

The confirmatory study did not show a difference between Adakveo (2.49, 95% CI [1.90, 3.26]) and placebo (2.30, 95% CI [1.75, 3.01]) in annualised rates of vaso-occlusive crises

→ Revocation of the conditional approval

Oxbryta and Casgevy – basis for positive B/R

Oxbryta (voxelotor) – full marketing authorisation

Increase from baseline in Hb levels >1 g/dL compared to placebo: 51.1%, vs. 6.5% respectively ($p<0.001$) at week 24, reductions in red blood cell breakdown.

Uncertainties: Does increase in Hb translates into better tissue oxygenation? Impact of Hb increase on (long-term) complications due to SCD?

Casgevy (exagamglogene autotemcel) – conditional marketing authorization

28 of 29 (96.6%) subjects achieved a continuous VOC free12-month period (VF12; 95% CI: 82.2%, 99.9%; $P < 0.0001$)

Uncertainties: small single-arm study, multiple major changes to study design, subjective elements in the primary endpoint definition, limited age range, long-term efficacy and safety (off-target editing)

Overview of the approved products : β-thalassemia

Invented name /EPAR link	INN	Outcome	Type of approval	Indication wording (abbreviated)	Outcome date
Ferriprox	Deferiprone	positive	Full MA	Treatment of iron overload	27/01/1999
EXJADE	deferasirox	positive	Full MA	Treatment of chronic iron overload	28/06/2006
Ferriprox	Deferiprone	positive	Full MA	In combination with another chelator (...) prevention or treatment of life-threatening consequences of iron overload	28/04/2016
Zynteglo	Betibeglogene autotemcel	positive	Conditional approval	Treatment of transfusion-dependent β-thalassaemia (TDT) *The marketing authorisation for Zynteglo has been withdrawn at the request of the marketing-authorisation holder on 24 March 2022.*	26/04/2019
Deferasirox Accord	deferasirox	positive	Full MA	Treatment of chronic iron overload	14/11/2019
Deferasirox Mylan	Deferasirox	positive	Full MA	Treatment of chronic iron overload	25/02/2021
Reblozyl	luspatercept	positive	Full MA	Treatment of anaemia	26/01/2023
Casgevy	exagamglogene autotemcel	positive	Conditional approval	Treatment of transfusion dependent β thalassemia	14/12/2023

Reblozyl and Casgevy – basis for positive B/R

Reblozyl (luspatercept) – full marketing authorization

RBC transfusion reduction of ≥ 33% (min. 2 units) from baseline to week 13-24 in 21% (48/224) in the luspatercept & BSC arm versus in 4.5% (5/112) in the placebo & BSC arm.
Uncertainties: absolute benefit modest, quality of life not improved, limited long-term data

Casgevy (exagamglogene autotemcel) – conditional marketing authorization

39/42 evaluable patients achieved transfusion independence lasting at least 12 months after exa-cel infusion, HbF levels were 7.8 (2.9) g/dL at Month 3, increased and were maintained with mean ≥10.9g/dL from Month 6 through the duration of follow-up

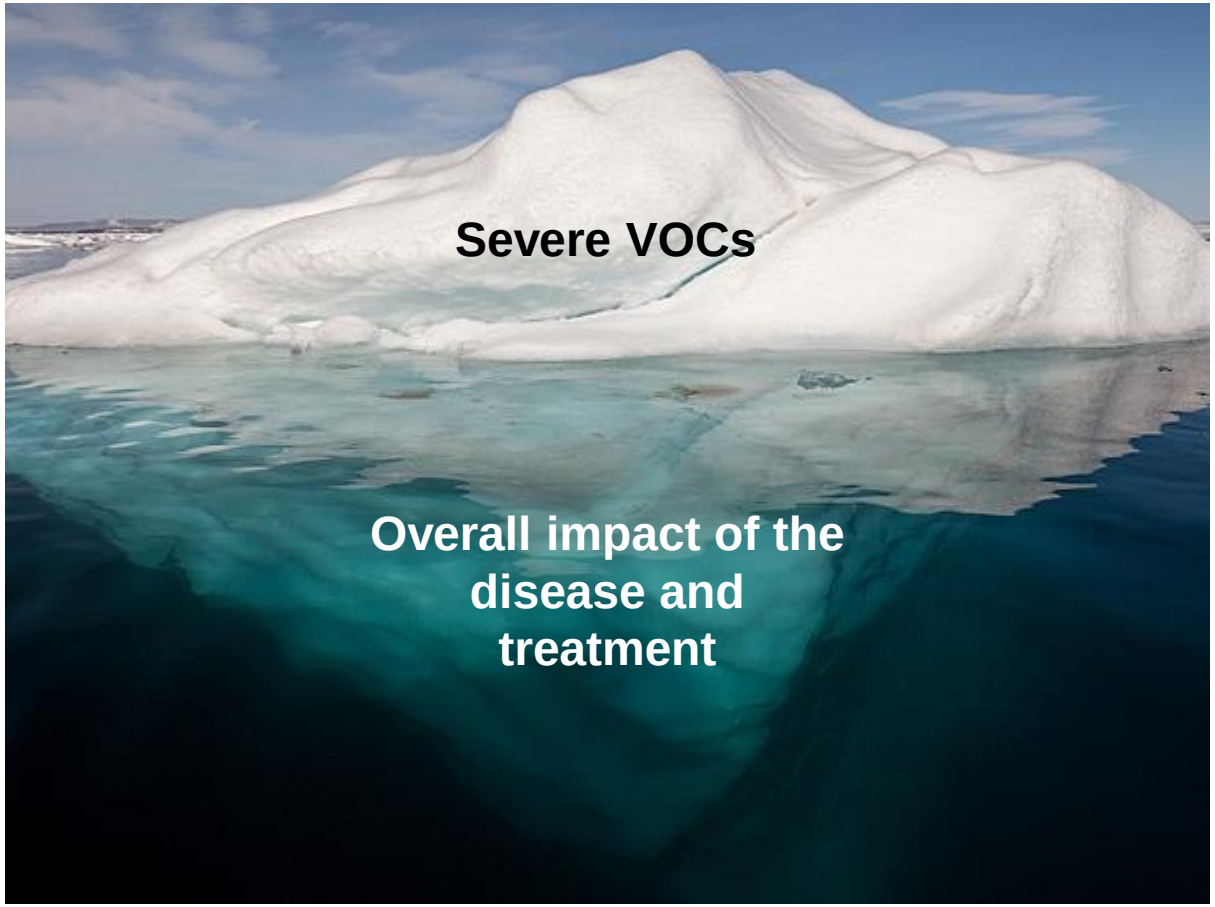
Uncertainties: small single-arm study, multiple major changes to study design, limited age range, long-term efficacy and safety

CHMP gives an opinion on benefit/risk

- Pricing / reimbursement are not considered
- ”Absolute” benefit risk – superiority to approved products not a requirement for regular marketing authorisation
  - Smaller (absolute) benefit also valuable if safety profile more tolerable /different, target population different etc.
  - The decision to use / not to use the product is for the patient and treating physician
  - A way to address the availability issues
- Unmet medical need a key component in decision-making, but does not overrule requirement for demonstration of positive B/R

Benefit: selection of endpoints

- Patient benefit is the most important goal
- Reliable, reproducible, quantifiable endpoints needed – especially in small / uncontrolled studies
- Example: severe VOCs in SCD
- ”Totality of evidence” – support from relevant secondary endpoints



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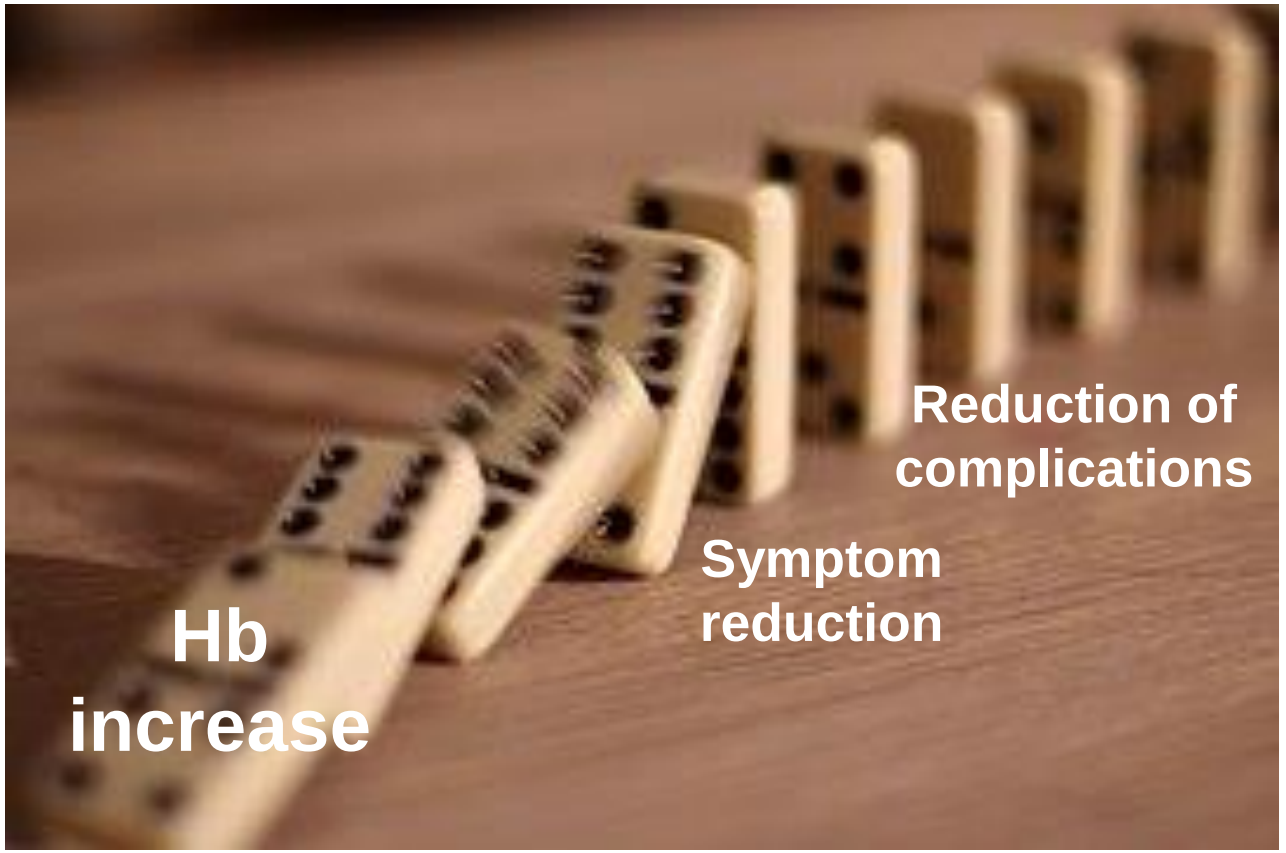
Benefit: selection of endpoints

- Patient benefit is the most important goal
- Reliable, reproducible, quantifiable endpoints needed – especially in small / uncontrolled studies
- Example: Hb increase in β thalassemia



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Challenges in bringing the patient perspective to benefit assessment

Patient benefit is the most important goal

Reliable quantification is challenging:

- Study design
  - single arm studies
  - open label study design
- (Unevenly) missing data
- Rare conditions, small studies
- Variation, fluctuation over time
- Impacted of external factors not related to the condition/treatment
- Required follow-up for resolution / reduction of long-term complications is long

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Thank you!