Voxelotor (GBT440) for The Treatment of Sickle Cell Disease

Lay Summary

Sickle cell disease (SCD) is a genetic disorder affecting red blood cells. In this disease, there is a change in the genes that encode haemoglobin, the protein that carries oxygen in red blood cells. This genetic change produces mutated haemoglobin molecules known as sickled haemoglobin (HbS). HbS molecules are found in slightly different shapes under different conditions, at low oxygen concentrations, HbS molecules are found in the Tense state (T-state) and at high oxygen concentrations, HbS molecules are found in the Relaxed state (R-state) which binds oxygen more strongly.

HbS molecules in the T-state, but not the R-state, bind to each other forming long fibres in a process known as polymerisation. When these fibres form inside a red blood cell, they stretch the cell, turning it sickle shaped. The sickle shaped red blood cells are unstable and often rupture. They also bind to the walls of small blood vessels and block them in a process known as vaso-occlusion, reducing blood and oxygen supply to tissues which causes a vaso-occlusive pain crisis.

The majority of available drugs treat the consequences of SCD, but not the disease itself. Voxelotor is the first approved drug in its class. It binds HbS molecules and shifts them to the R-state, which is unable to form fibres, thereby inhibiting polymerisation which is the root of SCD. There have been previous attempts to produce drugs that work the same way as voxelotor, but they did not succeed because they were not absorbed in the body when taken orally, did not bind HbS strongly and needed a very high dose to work. Voxelotor overcame these problems by binding HbS molecules more strongly, it is also rapidly absorbed into red blood cells.

Clinical trials showed that voxelotor is safe and treats some, but not all aspects of SCD. It reduced the rupturing of sickled red blood cells, however there was no evidence that it reduced the incidence of the vaso-occlusive pain crisis in SCD patients. There were also safety concerns that since voxelotor shifts HbS to the R-state, which binds oxygen more strongly, it would reduce oxygen release to tissues. However, there was no evidence to suggest that voxelotor impaired oxygen delivery. Voxelotor was approved for use in SCD patients aged ≥12 years. More studies are needed to evaluate its effects on vaso-occlusive crisis, further confirm its safety and expand its use to include children.

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1. Introduction

Voxelotor is a first-in-class disease modifying drug for sickle cell disease (SCD). It is an allosteric modifier which stabilises haemoglobin in the non-polymerising R-state to inhibit haemoglobin polymerisation, the key pathogenic event in SCD. After introducing the structure of haemoglobin and the pathophysiology of SCD, this review will discuss the rationale behind targeting haemoglobin polymerisation, describe the mechanism of action, development of voxelotor and present the evidence underpinning its use in terms of efficacy, safety and pharmacokinetics.

2. Sickle Cell Disease is Caused by Mutant Haemoglobin

2.1 Haemoglobin is a conjugated tetrameric protein that exhibits allosterism

Adult haemoglobin (HbA) comprises four globin chains, α and β chains, in the stoichiometry $\alpha_2\beta_2$[1] (**Figure 1A**). Each globin chain is conjugated with a haem moiety (**Figure 1B**) which binds a single oxygen molecule, allowing the transport of up to four oxygen molecules per haemoglobin. The haem complex consists of a porphyrin derivative coordinating an iron ion (Fe^{2+}) in a tetradentate arrangement. The iron ion is further coordinated by a histidine residue (His F8) which links it to a globin chain. The last coordination site is occupied by oxygen[2–4] .

Oxyhaemoglobin and deoxyhaemoglobin exist in different conformations, designated as the Relaxed (R) state and the Tense (T) state respectively[5]. The R state exhibits higher oxygen affinity and predominates at higher oxygen pressure[3,6] (**Figure 2A**). This phenomenon was explained by the Monad-Wyman-Changeux (MWC) allosterism model[7,8], which postulates that an oligomer exists in a structural T⇋R equilibrium, and that subunit symmetry is conserved such that no oligomer contains R and T subunits simultaneously[2] (**Figure 2B**). Allosteric modulators shift the T⇋R equilibrium by preferentially binding one conformation, oxygen also induces a conformational change in haemoglobin towards the R-state[5,6,8,9] (**Figure 2C**). The MWC model and haemoglobin's conformational are the basis behind the mechanism of action of voxelotor.

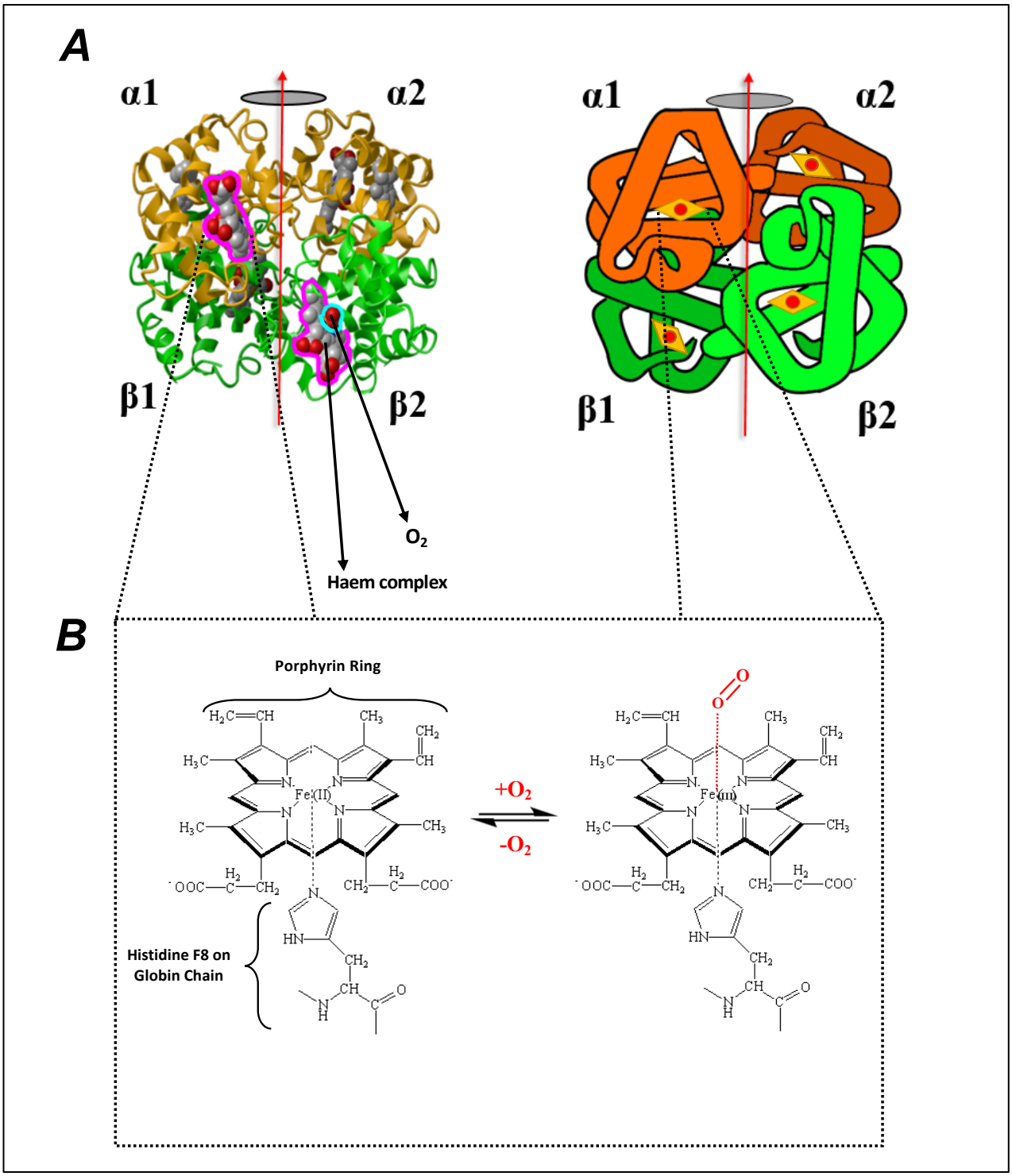

Figure 1 | The structure of haemoglobin. (A) Ribbon diagram and sketch based on the crystal structure of human oxyhaemoglobin (PBD ID 2DN1)[4], illustrating that haemoglobin is as a dimer of αβ protomers[2], two haem complexes are outlined in magenta with an oxygen molecule bound outlined in cyan. **(B)** The structure of the haem moiety* illustrating oxygen binding. The Fe^{2+} ion forms six bonds within the haem complex[3] four with the tetrapyrrole ring and one with His F8 (His87 & His92 on the α and β chains respectively)[9] which tethers the Fe2+ ion to its respective globin chain. The final bond is formed when an oxygen molecule binds the final coordination site as an axial ligand.

* Chemical structure adapted from Purdue University: http://chemed.chem.purdue.edu/genchem/topicreview/bp/1biochem/blood3.html

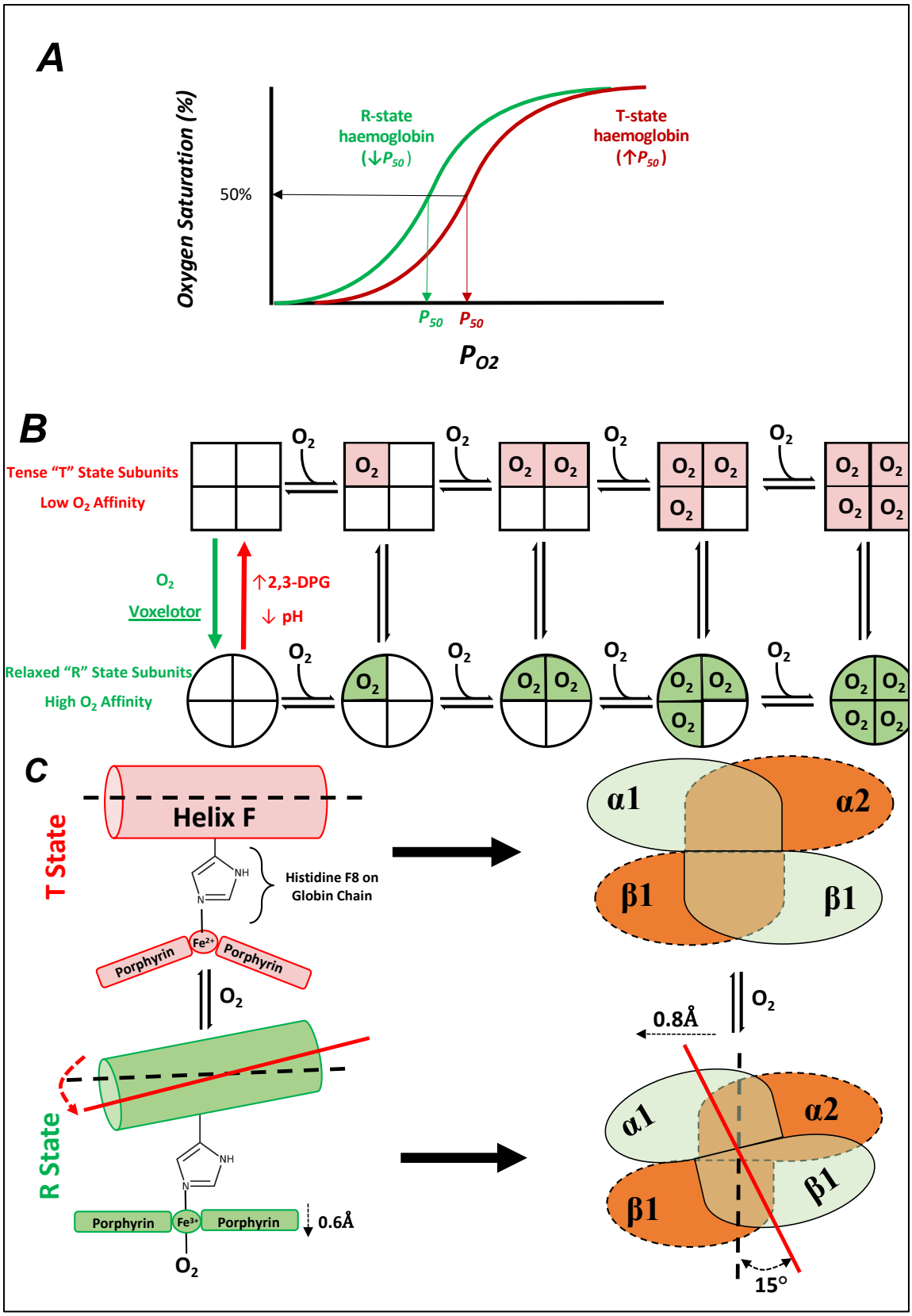

Figure 2 | The structural conformations of haemoglobin as explained by the MWC model. (A) The R state of haemoglobin exhibits higher oxygen affinity, achieving 50% oxygen saturation at lower PO2 comparing to the T state. **(B)** The MWC model of allosterism[7], haemoglobin exists in a structural equilibrium between the T and R states, the symmetry of subunits is conserved. Oxygen and Voxelotor promote R state formation. **(C)**The conformational change in the T → R transition. In the T state, the porphyrin ring is dome-shaped and Fe^{2+} protrudes 0.6Å outside the ring plane[2]. Oxygen binding flattens the porphyrin ring, bringing the Fe^{2+} ion within the ring plane[9] this exerts a pull via His F8 on Helix F of the globin chain which alters the quaternary structure. The α1β1 promoter thence rotates by 15° and translates by 0.8 Å[6,8,10]. This mechanism is tightly coupled such that the binding of a single O2 molecule shifts all subunits to the R state[2].

2.2 Sickle cell disease is caused by a missense mutation in the β-globin chain

The point mutation (GAG→GTG) results in the substitution of charged glutamic acid with hydrophobic valine at the sixth position in the β-chain (β^S allele), producing sickled haemoglobin (HbS)[11]. Under deoxygenation, in the T-state, hydrophobic motifs on individual HbS tetramers are exposed, causing the HbS molecules to bind to each other via the mutant Val6 residue thereby forming a polymer[12]. As the intra-erythrocytic HbS polymers extend they deform the erythrocytes into sickle-shaped cells[13–15], which are prone to aggregation and haemolysis[13,16]. Sickled erythrocytes are susceptible to entrapment within the micro-circulation, leading to a vaso-occlusive crisis (VOC), which is the hallmark of SCD[12,13] (**Figure 3A**). Following sickling and vaso-occlusion, SCD manifests a plethora of acute and chronic complications affecting multiple systems (**Figure 3B**).

SCD is an umbrella term for a group of inherited disorders which contain at least one β^S allele [13,14] inherited as an autosomal co-dominant trait[17]. Sickle cell anaemia (β^S/β^S homozygosity) is the most common and severe form[14,18]. SCD is modulated by genetic and non-genetic factors[16], resulting in phenotypic variation between individuals in which there is a difference in the relative manifestation of pathological processes such as the haemolytic and vaso-occclusive subphenotypes[13,15]. The phenotypic complexity of SCD poses a potential challenge to the efficacy of disease-modifying drugs such as voxelotor.

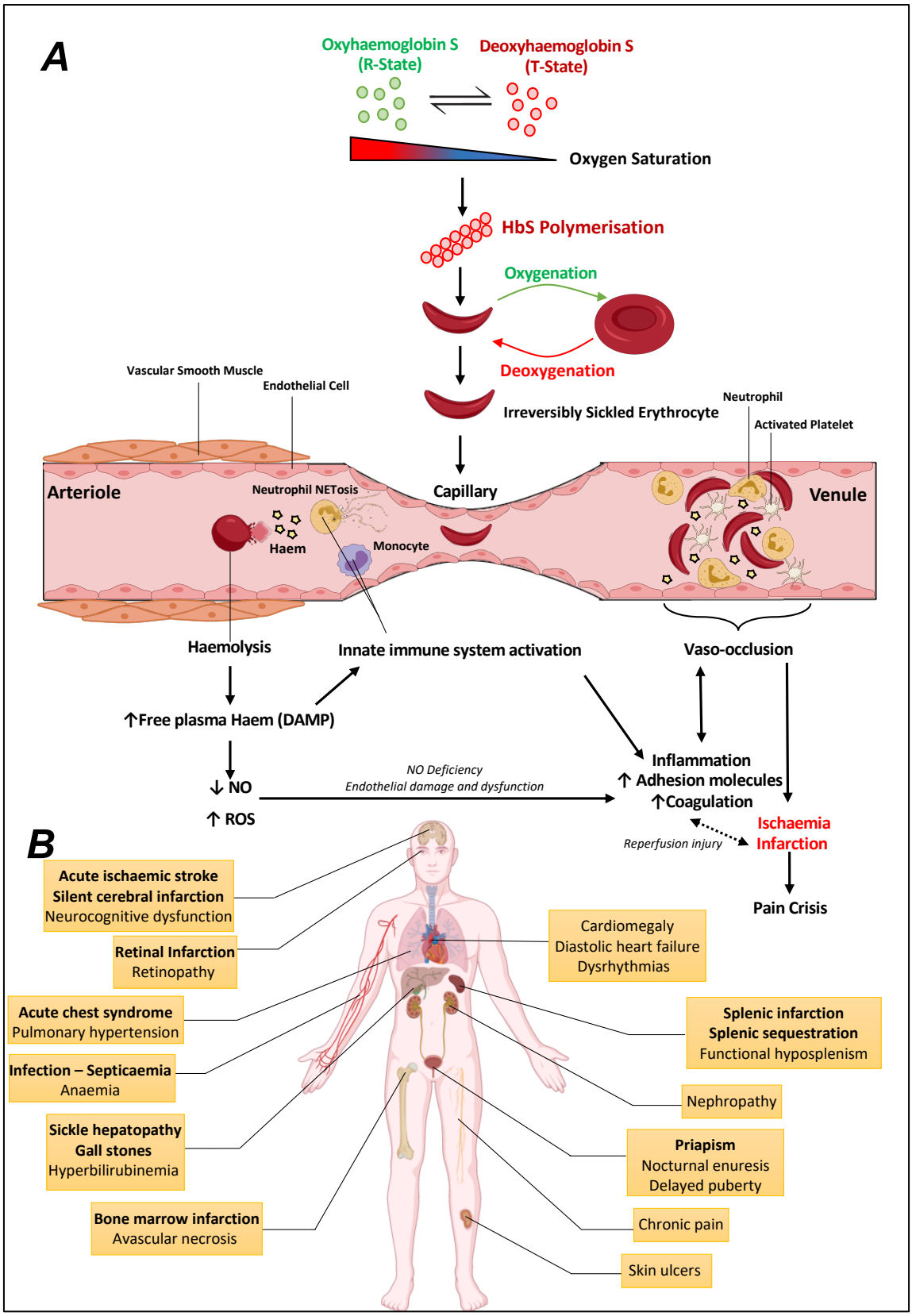

Figure 3 | SCD pathophysiology and clinical complications. **(A)** Following deoxygenation, HbS tetramers containing mutant β subunits shift to the T-state and thence polymerize. The polymer bundle distorts the erythrocyte cell membrane forming sickled cells. The process of sickling and unsickling is initially reversible[13,18], however an irreversibly sickled erythrocyte then forms due to increased membrane rigidity[19]. The sickled erythrocytes are rheologically impaired and over-express adhesion molecules09/01/2021 22:55:00, thereby aggregating with platelets, neutrophils and endothelial cells leading to vaso-occlusion and ischaemia. Sickled erythrocytes are unstable and prone to haemolysis, releasing haem which is a potent damage-associated molecular pattern (DAMP) triggering a proinflammatory innate immune response[13,14]. Haem also causes endothelial dysfunction by scavenging nitric oxide[23] and producing reactive oxygen species (ROS), exacerbating vaso-occlusion[13]**. (B)** SCD exhibits multi-system clinical consequences, acute conditions are written in bold. Pain is the most common complication. (Diagrams created via BioRender).

3. Voxelotor Inhibits Haemoglobin S Polymerisation

3.1 Targeting haemoglobin polymerisation

Current SCD treatments mainly ameliorate the downstream sequelae of symptoms. The disease-modifying agents approved for SCD target aggregation (Crizanlizumab) or oxidative stress (L-glutamine), however these events are not the key initiators of the pathological cascade (**Figure 3B**). This necessitated drugs that interdict the root cause of the disease: deoxyhaemoglobin S polymerisation[12,24,25]. HbS polymerisation inhibition can be achieved via several strategies[26]. However, none have yielded clinically approved drugs, with the exception of hydroxyurea, a cytotoxic drug that acts by increasing the levels of the non-polymerising fetal haemoglobin (HbF). Hydroxyurea is myelosuppressive[27], not equally efficacious in patients with low baseline HbF, and the increase in HbF subsided over time[27–29].

Complete inhibition of HbS polymerisation is not required for efficacy[26,30,31]. HbS polymerisation follows a double nucleation mechanism[32], whereby a delay phase precedes polymerisation onset, followed by abrupt polymer growth[33]. The delay time is inversely proportional to deoxyhaemoglobin S concentration to the 30th power[34]. Thus, merely a small degree of HbS polymerisation inhibition translates into a large increase the delay time, sufficient to allow erythrocytes to escape capillaries before the onset of polymerisation and sickling[26,35].

3.2 Voxelotor stabilises the non-polymerising R-state of haemoglobin

Voxelotor is an allosteric modifier which shifts the T⇋R equilibrium towards the high O_2 affinity R-state by stabilising it, thereby increasing the proportion of oxyhaemoglobin during postcapillary venule transit to prevent sickling[36,37]. The rationale behind HbS allosteric modulators is derived from the key fact that *only the deoxygenated, low O_2 affinity, T-state conformation of haemoglobin S is polymerisable*[2,38,39] (**Figure 4A**). Solubility experiments have shown that only the T-state HbS is incorporated into the polymer whereas the R-state is excluded[2,38,39]. This is in part due to the absence of a hydrophobic pocket in the R-state HbS[2], which acts as an acceptor site for the mutant Val6 in an adjacent HbS tetramer (**Figure 4B**). Furthermore, HbS exhibits reduced oxygen affinity[40] favouring the polymerising T-State thereby exacerbating sickling. These principles rationalised the use of allosteric modulators in the treatment of SCD, which act by stabilising the R-state and increasing O_2 affinity to impede HbS polymerisation under hypoxia and hence sickling.

Voxelotor interacts with both α-globin chains, resulting in 1:1 binding stoichiometry to HbS. It forms a reversible Schiff base linkage to the N-terminal valine of one of the α-globin chains and forms a hydrogen bond to Ser131 of the second α chain[36,37] (**Figures 5A-B**). The hydrogen bond prevents the binding of a second voxelotor molecule to the free N-terminal valine of the remaining α chain, achieving 1:1 binding stoichiometry[36,37]. Upon binding haemoglobin, voxelotor induces a conformational change in the intra-dimer interface and haem pockets, increasing O_2 affinity without compromising O_2 release[41]. Voxelotor's mechanism of action was demonstrated by a leftward shift in the oxygen equilibrium curve (**Figure 5C**) and increasing the proportion of oxyhaemoglobin under hypoxia (**Figure 5D**).

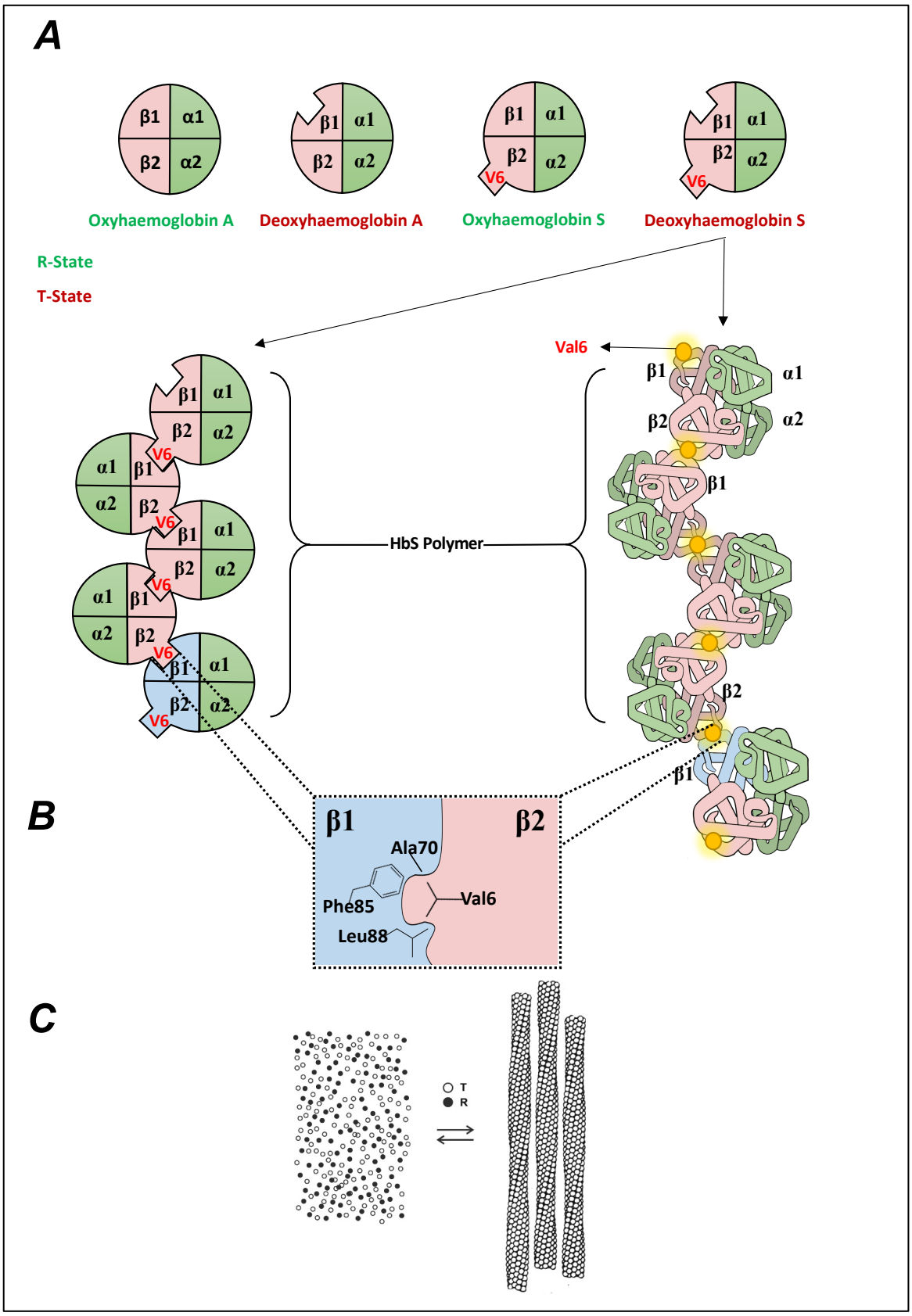

Figure 4 | The formation of deoxy HbS polymers. **(A)** Diagrammatic representations of Adult (A) and Sickled (S) haemoglobin. Sickled haemoglobin exhibits a mutant Val6 residue on the β2 chain[11]. In the deoxy T state, a hydrophobic cavity is exposed on the β1 chain which binds Val6 but not the naturally occurring Glu6 residue. **(B)** The interaction between HbS tetramers within the polymer. The mutant Val6 residue binds a hydrophobic cavity comprising Ala70, Phe85 and Leu88[2,36], this cavity is absent in oxyhaemoglobin[2]. Consequently, only deoxyhaemoglobin S is capable of polymerising. **(C)** Sketch depicting an HbS fibre, illustrating that only T state Hb is incorporated into the polymer, a shift towards the R-state would impede polymerisation. (Figure 4C is from Henry *et al.* 2020)

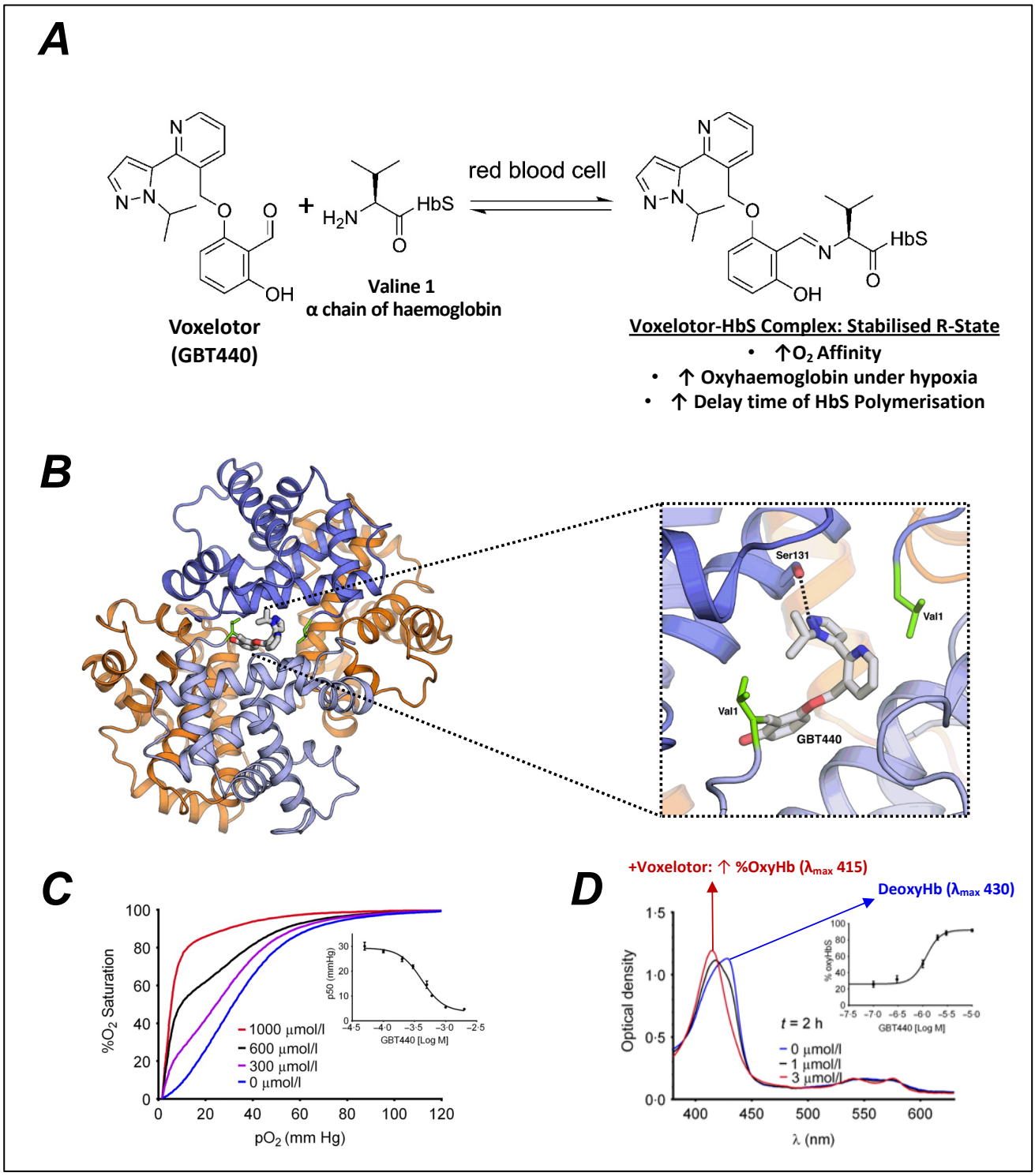

Figure 5 | The mechanism of action of Voxelotor. **(A)**Voxelotor forms a Schiff base linkage with the N-terminal valine of the alpha chain thereby stabilising the R state. **(B)** The crystal structure of Voxelotor complexed with HbS, illustrating 1:1 binding stoichiometry. α and β chains shown in blue and orange respectively, the N-terminal valine is shown in green. The enlarged view shows Voxelotor within its binding site, forming simultaneous Schiff base linkage to the N-terminal valine of one α chain and a hydrogen bond to Ser131 of the other α chain, which prevents the binding of a second Voxelotor molecule. **(C)**The oxygen equilibrium curve from a whole blood of a SCD patient. Incubation with increasing concentrations of Voxelotor increases Hb-O_2 affinity as evident from a leftward shift. The inset illustrates that Voxelotor dose dependently reduces the P50 value (EC_{50} = 415 ± 15 µm/l). **(D)** Graph illustrating HbS visible spectra following 2 hours of deoxygenation and addition of different concentrations of Voxelotor. Addition of Voxelotor increased the proportion of OxyHbS (λ_{max} 415) relative to deoxyHbS (λ_{max} 430) as evident in a leftward shift in the peaks. The inset shows that Voxelotor dose-dependently increases %oxyHbs (EC_{50} 1.2 ± 0.03 µmol/l). (Data and figures are from Oksenberg *et al*. 2016)

4. Development of Voxelotor

Prior to Voxelotor, several anti-sickling agents have been identified to allosterically increase haemoglobin's O_2 affinity, including aromatic aldehydes such as the naturally occurring 5-Hydroxymethylfurfural (5-HMF)[42], velaresol and tucaresol[43] (**Figure 6**). These compounds provided a proof of concept by inhibiting HbS polymerisation and reducing haemolysis without compromising O_2 delivery, however they exhibited poor pharmacokinetics. Velaresol is not orally bioavailable, with a short action duration of 3-4 hours following intravenous infusion[44,45]. Tucaresol, although orally bioavailable, poorly partitions into the RBC compartment[46,47], leading to high plasma concentrations and was subsequently terminated due to immunotoxicity[48]. 5-HMF reached clinical trials but was not granted approval hitherto.

Metcalf *et al.* developed voxelotor through a number of structural-activity relationship (SAR) studies based on previously characterised HbS allosteric modifiers to achieve greater potency and more favourable pharmacokinetics[36]. The resultant compounds (**1**-**5**) following the SARs leading to voxelotor are shown in **Figure 6.** In hemoximetry assays, compound **1** was shown to increase Hb-O_2 affinity. Similar to 5-HMF, **1** forms a Schiff base to the N-terminal valine of each α chain, with the aromatic rings filling the interdomain cavity. The B-ring of **1** was replaced with a fused bicyclic analogue, to achieve greater dipole interactions between the rings and fill the interdomain cavity more efficiently, producing **2,** which exhibited a faster on-rate. The A-ring of **2** was replaced with a pyridine analogue to reduce metabolic liability, producing **3**. The methoxypyridine A-ring of **3** was subsequently retained, and SARs were carried out on the B-ring, yielding **4** which demonstrated greater potency and delayed HbS polymerisation *in vitro*. Final A-ring SARs were then carried out leading to the discovery of **5** which exhibits a phenolic A-ring that conferred greater potency, increased polymerisation delay time, and prolonged the drug's half-life due to stronger intramolecular hydrogen bonding, owing to the phenolic hydroxyl group.

Compound **5** demonstrated favourable pharmacokinetics and a half-life suitable for once-daily dosing[37]. Unlike its predecessors, it rapidly partitions into the RBC compartment, with an RBC:Plasma ratio of ~150:1[37]. **5** binds Hb in a 1:1 stoichiometry in contrast with previously characterised compounds which exhibit a 2:1 stoichiometry (**Figure 5B**). After demonstrating an ideal combination of potency and pharmacokinetics, **5** was identified as **GBT440 (voxelotor).**

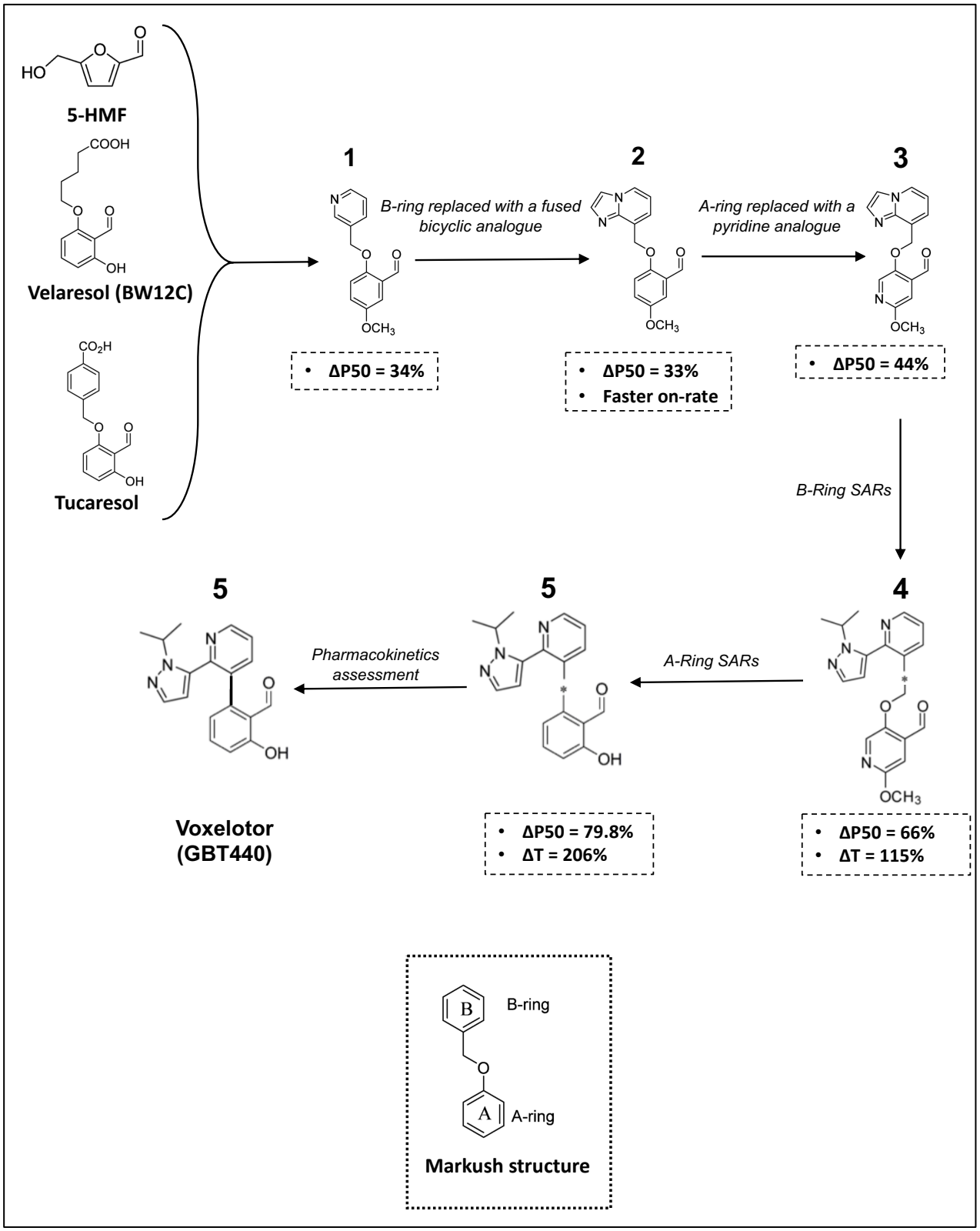

Figure 6 | Summary of the SARs and medicinal chemistry results of Metcalf *et al*. Voxelotor was developed via a number of SARs and chemical modifications based on previously discovered anti-sickling agents to achieve more favourable pharmacokinetics. A markush structure is shown which illustrates the A and B-Rings. The potencies of the compounds are measured as %ΔP50, the % change from baseline PO_2 at which purified HbS (25μm) is 50% saturated with O_2 following the addition of the compound(30 μm). A polymerization assay was carried out on compounds **4** and **5**, %ΔT denotes the % change from baseline delay time of HbS (50μm) following the addition of the compound (75μm). (Chemical structures and data are from Metcalf *et al.* 2016).

In comparison with its predecessors, voxelotor introduced various improvements. Haemoglobin exists at an RBC concentration of 5mM[36,45] with ~250x10^6 Hb molecules per RBC, in contrast to conventional drug targets such as enzymes and cell surface receptors which exist at ~10^3 per cell[31]. This requires high drug concentration to target haemoglobin, indeed, 5-HMF inhibited sickling in the mM range[42]. In contrast, the 1:1 binding stoichiometry of voxelotor, facilitated by its higher Hb selectivity and rapid partitioning into RBCs achieves greater Hb saturation at lower doses and mitigates off-target effects. And as previously discussed, complete HbS saturation is not required to achieve therapeutic utility, voxelotor exhibits 26.5% Hb saturation at therapeutic doses[49]. These properties were consistent in that voxelotor exhibited higher potency than its predecessors[37].

5. Efficacy and Safety of Voxelotor

5.1 Clinical trials

The preliminary efficacy of voxelotor was established through a Phase 1/2, double-blind, placebo controlled ascending dose trial[50]. Haemolysis markers such as haemoglobin, unconjugated bilirubin, reticulocyte and sickled RBC levels were used as surrogates for efficacy. The study included a 90-day dosing period (n=16) where patients were given either 700mg/day, 900mg/day voxelotor or placebo. A pooled comparison between patients receiving voxelotor (700-900 mg/day) and placebo revealed a significant increase in median Hb (1 vs -0.1 g/dL). There was also a significant decrease in sickled RBCs and haemolysis markers such as % reticulocytes and unconjugated bilirubin comparing to placebo. A subsequent 6-month open label extension revealed that the improvements were durable throughout. Due to the small sample size, a larger, longer term confirmatory clinical trial was needed.

The HOPE trial led to the approval of voxelotor. The trial was a phase 3, double-blind, randomized, placebo-controlled trial[49]. The trial enrolled 274 SCD patients, aged 12-65. Patients were given 1500mg/day (n=90) or 900mg/day (n=92) voxelotor or a placebo (n=92). The primary outcome measure was a haemoglobin response defined as a >1g/dL increase at week 24. Secondary efficacy endpoints included haemolysis markers and annualized VOC rates. A haemoglobin response occurred in a greater proportion of patients in the 1500mg/day group (51%) compared to placebo (7%) regardless of concurrent hydroxyurea use or baseline anaemia severity. Furthermore, there was a significant ($P<0.001$) decrease from baseline in indirect bilirubin levels (-29.1% vs. -3.2%) and reticulocyte levels (-19.9% vs. +4.5%) in the 1500-mg group comparing to placebo. However, there was no significant difference in the annualized VOC incidence rates, 2.77 and 3.19 VOC per person-year in the 1500mg group and placebo respectively. Regardless of the lack of clinical outcomes and short duration of the trial, voxelotor was granted FDA approval for SCD in patients aged ≥12 years[51], whilst being granted several designations in the process[52–56] (**Figure 7**).

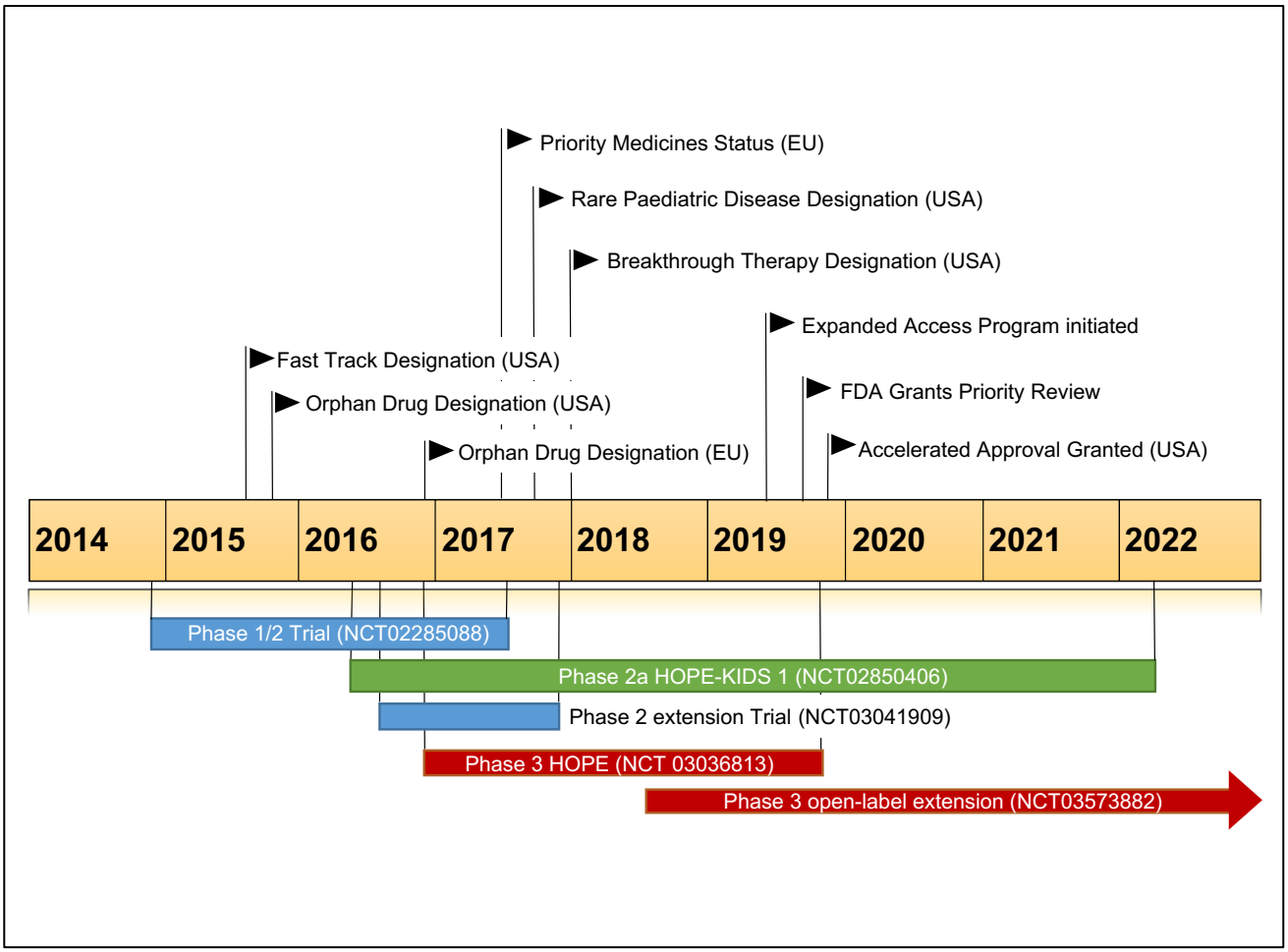

Figure 7 | Key designations granted to voxelotor leading up to its FDA approval. (Redrawn and adapted from Blair 2020)

Voxelotor's approval was debated. The HOPE trail relied on surrogate end points and failed to demonstrate a significant reduction in VOC incidence, which is the hallmark of SCD. Investigators argued that a mere reduction in haemolytic markers without ameliorating clinical severity is inadequate evidence for efficacy[57]. The HOPE trial was also disadvantaged for lacking neurovascular imaging as there were safety concerns that voxelotor may compromise tissue oxygenation and cause silent cerebrovascular events[57]. On the contrary, it is argued that chronic haemolysis is an independent predictor of organ damage, stroke and SCD mortality, such that for every 1 g/dL reduction in Hb the risk of ischaemic stroke increases by nearly two fold, thus justifying the approval of voxelotor based on reduction in haemolytic markers[58,59].

A number of ongoing trials are investigating voxelotor (**Table 1**) to evaluate its safety over extended periods and characterise its effects on VOC rates to address the limitations of the HOPE trial. Voxelotor is being expanded for use in paediatric patients, demonstrating efficacy in the phase 2a HOPE-Kids 1 trial[60].

Title acronym (Identifier)	Population	Design	Primary outcome measures	Expected completion
(NCT03573882)	SCD patients aged ≥12 years previously participated in the **GBT_HOPE** trial	Phase 3, open label extension, single arm	• TEAE over a 5-year period • Frequency of SCD-related complications over 5 years	Oct 2024
(NCT04247594)	SCD patients aged 18-60	Phase 2, open label, sequential assignment, dose escalation	• TEAE in patients receiving 1500-3000 mg/day Voxelotor	Dec 2021
(NCT04188509)	Paediatric SCD patients aged 4-19 previously participated in Voxelotor trials	Phase 3, open label, single arm	• TEAE and SAE • Frequency of SCD-related complications	Jan 2026
(NCT04581356)	SCD patients aged >12 years	Phase 4, open label, single arm	• Change in peak O_2 consumption (VO_2) after Voxelotor treatment	Aug 2021
ActIVe (NCT04400487)	SCD patients aged 12-55	Phase 4, open label	• Change in total daily activity nocturnal sleep, wake time, sleep efficiency and Hb-O_2 saturation	Sep 2021
HOPE Kids 1 (NCT02850406)	Paediatric SCD patients aged 9 months – 17 years	Phase 2a, open label, sequential assignment, dose escalation	• Part A: PK profile of Voxelotor in patients aged 6-17 • Part B: Change in Hb in patients aged 4-17 • Part C: Change in cerebral blood flow in patients aged 4-17 • Part D: TEAE and SAE in patients aged 9 months – 4 years	Dec 2022
HOPE Kids 2 (NCT04218084)	Paediatric SCD patients aged 2-15	Phase 3, randomized, double-blind, placebo-control	• Change in mean velocity arterial blood flow as measured by transcranial Doppler ultrasound	March 2026

Table 1 | Ongoing clinical trials investigating Voxelotor. (Abbreviations: TEAE, treatment emergent adverse events. SAE, severe adverse events. PK, pharmacokinetics)

5.2 Safety profile

Voxelotor was well tolerated throughout clinical trials. A summary of the safety results based on the HOPE trial[49] is shown in **Table 2.** Adverse events were similar amongst both arms, nausea and diarrhoea being the most common. Most events were grade 1 or 2 and determined to be unrelated to voxelotor or placebo. The proportion of grade ≥ 3 events being also similar in both groups. A similar safety profile was obtained in paediatric patients in the HOPE Kids 1 trial[60]. Administration of voxelotor at supratherapeutic concentrations was not associated with QT interval prolongation[61].

A theoretical concern associated with voxelotor is that the increased Hb-O_2 affinity may cause tissue hypoxia[62]. However, Voxelotor neither elevates erythropoietin levels nor increases reticulocyte count[49,63], which is inconsistent with hypoxia. It was also shown to have no effect on exercise capacity[50,64]. Contrarily, voxelotor is thought to cause a net increase in O_2 delivery, via elevating Hb levels by reducing haemolysis and blood viscosity[37]. This concern requires further evaluation.

Incidence, (%)	Voxelotor 1500 mg *(*n=88)	Placebo (n=91)
SCD-unrelated TEAE	94%	89%
SCD-related TEAE	76%	72.5%
TEAE leading to discontinuation	9.1%	4.4%
TEAEs occurring in ≥10% patients		
Headache	26%	22%
Diarrhoea	20%	10%
Nausea	17%	10%
Arthralgia	15%	12%
Upper respiratory tract infection	14%	11%
Abdominal pain	14%	8%
Fatigue	14%	10%
Rash	14%	10%
Pyrexia	12%	7%

Table 2 | The percentage of events reported in the HOPE trial. (Abbreviations: TEAE, treatment emergent adverse event).

6. Pharmacokinetics of Voxelotor

Voxelotor exhibits a linear pharmacokinetic profile. Following oral administration, it is rapidly absorbed with an oral bioavailability of >35%[65], reaching a peak plasma and whole blood concentration after 2 and 6 hours respectively[66]. Steady state is reached within 8 days after repeated administration. The terminal half-life is shorter in SCD patients (35.5 h[61] - 50 h[63]) than in healthy individuals (61-85 h)[63]. Voxelotor rapidly partitions into RBCs with an RBC:Plasma ratio of 67-111:1[63], the apparent volume of distribution in the central and peripheral compartment is 338L and 72L in plasma, respectively[61].

Voxelotor is metabolised through Phase I (oxidation and reduction) and Phase II (glucuronidation) metabolism. Oxidation is mediated primarily via CYP3A4, with minor contributions CYP2B6, CYP2C9 and CYP2C19. Concomitant use of Voxelotor and fluconazole is contraindicated[61].

Administration of radiolabelled Voxelotor revealed that 62.6% of the dose is excreted in faeces (33.3% unchanged) and 35.4% is excreted in urine (0.08% unchanged). Hepatic metabolism is the major elimination route, as two-thirds is excreted as metabolites[66]. Voxelotor is well-tolerated in patients with severe renal impairment however a dose-adjustment is required for patients with severe hepatic impairment[65].

7. Future prospects and conclusion

Voxelotor is a first-in-class treatment which targets haemoglobin polymerisation, the primary pathogenic event in SCD. It has bypassed several challenges that faced the development of its predecessors to attain more favourable pharmacokinetics and pharmacodynamics. The evidence leading to Voxelotor's approval, based on reduction in haemolytic markers, suggests that it is likely to benefit SCD patients of the haemolytic subphenotype. Further studies are warranted to investigate its effects on clinical outcomes such as vaso-occlusive crises and confirm that it confers no risk of hypoxia.

The limited repertoire of approved SCD drugs has been a constant challenge, recently exacerbated during the COVID-19 pandemic where SCD patients are prone to poor prognosis following SARS-CoV-2 infection[67]. Indeed, Voxelotor may be used alongside other SCD drugs, each targeting a different pathogenic event within the SCD cascade, to potentially achieve an additive therapeutic effect. Voxelotor has been efficacious in treating a SCD patient suffering from COVID-19, being used in lieu of transfusions[68].

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