Published in final edited form as:
Br J Haematol. 2014 February ; 164(3): 456–458. doi:10.1111/bjh.12635.

A phase 2 study of HQK-1001, an oral fetal haemoglobin inducer, in β-thalassaemia intermedia

Adlette Inati[1,2], **Mario Kahale**[2], **Susan P. Perrine**[3], **David H.K. Chui**[3], **Ali T. Taher**[4], **Suzanne Koussa**[5], **Therese Abi Nasr**[5], **Hussein Abbas**[4], and **Richard G. Ghalie**[6]

[1]Lebanese American University, Beirut, Lebanon

[2]Rafik Hariri University Hospital, Beirut, Lebanon

[3]Boston University School of Medicine, Boston, MA

[4]The American University of Beirut Medical Centre, Beirut, Lebanon

[5]Chronic Care Centre, Beirut, Lebanon

[6]HemaQuest Pharmaceuticals, San Diego, CA

Keywords

Anaemia; β-thalassaemia; clinical trials; gene expression; fetal haemoglobin; haemoglobinopathies

The β-thalassaemia syndromes represent a World Health Organization-designated global health burden (Weatherall *et al*, 2010). Reactivation of fetal globin (HbF) expression is a rational therapeutic approach in inherited β-globindisorders, because the fetal *HBG*(γ-globin genes) are universally present and appropriately contextually integrated in the *HBB*(β-globin gene) locus in haematopoietic stem cells (Bauer *et al*, 2012). The defective production of β-globin chains in β-thalassaemia can be compensated for by an increase in γ-globin chains, which pair with α-globinchains to form HbF, thereby decreasing the α/non α-globin imbalance, the hallmark of β-thalassaemia. Several classes of HbF inducers have been investigated in β-thalassaemia, including cytotoxic agents, DNA methyl transferase inhibitors, histone deacetylase (HDAC) inhibitors including short chain fatty acids, thalidomide derivative, and erythropoietin, but no consistently effective agents have been identified (Musallam *et al*, 2013).

The short chain fatty acids arginine butyrate, sodium phenylbutyrate, and isobutyramide were shown to increase HbF in β-thalassaemia and sickle cell disease, but had to be administered intravenously or by large oral daily doses, which is not practical for widespread long-term use (Perrine *et al*, 1993; Collins *et al*, 1995; Capellini *et al*, 2000). The orally bio available butyrate derivative 2,2-dimethylbutyrate sodium salt (HQK-1001) does not exhibit HDAC2 inhibitory activity and stimulates *HBG* expression and erythropoiesis in animal models and *in vitro* at concentrations readily achievable in humans(Pace *et al*, 2002; Mankindy *et al*, 2006). In a proof-of-concept study, HQK-1001 at

Correspondence: Dr R G Ghalie, Chief Medical Officer, HemaQuest Pharmaceuticals, 11995 El Camino Real, Suite 302, San Diego, CA 92130, USA, Tel: +1.858.356.5583, Fax: +1.858.356.5579, rghalie@hemaquest.com.

Authorship: AI, SP, and RG designed the research; AI, MK, AT, SK and TA performed research; DC and HA performed genetic studies; RG and SP analysed the data and wrote the manuscript; AI and SP revised the manuscript.

Conflict of interest disclosure: SP is founder and equity owner and RG is an employee of HemaQuest Pharmaceuticals. The other authors declare no competing financial interests.

10, 20, 30, and 40 mg/kg administered daily for eight weeks in 21 subjects with non-transfusion dependent β-thalassaemia was well-tolerated (Fuchareon *et al*, 2013). HQK-1001 at 20 mg/kg, which provided the best results, increased HbFin 8 of 9 subjects with a median increase of 6.6% and 4.4 g/l, and increased total haemoglobin in 4 of 9 subjects by a mean of 11 g/L. Here, a single-centre study was conducted to evaluate HQK-1001 at 20 mg/kg/day administered for a longer period (NCT01642758).

Adult patients with β-thalassaemia intermedia characterized by two β-globin mutations were eligible if their haemoglobin was between 60 and 90 g/l on two occasions during the 30-day screening period. Patients were excluded if they were transfused within the previous three months, received iron chelation agents within the previous seven days, another investigational agent within the previous 30 days, erythropoietic agents within the previous 90 days, or hydroxycarbamide within the previous six months, or had pulmonary hypertension requiring oxygen therapy, alanine aminotransferase (ALT) > 4 times the upper limit of normal, or serum creatinine > 135 μmol/l. HQK-1001 capsules (HemaQuest Pharmaceuticals, San Diego, CA) was administered at 20 mg/kg once daily for 24 weeks. Folic acid was given daily, and to prevent iron-deficient inefficient erythropoiesis, oral iron was given if serum ferritin was < 1500 pmol/l, but stopped if ferritin levels were > 2250 pmol/l. After signing an Ethics Committee approved informed consent form, subjects were assessed clinically and underwent laboratory tests twice during a 30-day screening period, every four weeks while receiving HQK-1001, and then four weeks after the end of dosing.

Ten subjects were enrolled, seven male and three female, with a mean age of 29.4 years (range 18-52 years). Eight subjects were splenectomized; two had palpable splenomegaly at 4 and 7 cm below the left costal margin. The mean (range) baseline values were: HbF26.6% (7.9–73.8%), absolute HbF 20.1 g/l (5.5–53.9 g/l), total haemoglobin 77.4 g/l (61.5–96.0 g/l), platelet count 782 × 10^9/l (486-1039 × 10^9/l), reticulocytes 10.9% (7.1–15.7%), and serum ferritin 3188 pmol/l (375–9772 pmol/l).

Nine subjects completed the study and one subject was discontinued at Week 16 because of worsening anaemia requiring a transfusion. Mean compliance with HQK-1001, calculated as the ratio of the number of HQK-1001 capsules taken divided by the number of capsules prescribed, was 92.5%; two subjects had compliance <90%. Treatment was generally well-tolerated. All adverse events, except one case of vertigo, were graded as mild or moderate, and were reversible. Fatigue was the most common adverse event, reported in 3 subjects. In contrast, 5 subjects reported increased activity and improved mood. Two subjects each reported nausea, epigastric pain, dyspepsia or fever. The most common laboratory abnormalities were mild and reversible increases in aspartate aminotransferase (AST) in five subjects and in ALT in four.

HbF increased in all subjects, with peak increase occurring after a mean of 14 weeks of therapy; the mean (range) increase from baseline was 4.8% (2.3–9.8%) for HbF % ($p = 0.0006$) and 3.19 g/l (0.5–6.6 g/l) for absolute HbF ($p = 0.001$). Total haemoglobin increased in 7 subjects, with a mean increase of 4.7 g/l (range 1.0–10.0 g/l). Figure 1 shows the baseline and peak value by subject for HbF and total haemoglobin. Table I presents each subject's thalassaemia mutations and polymorphisms for 3 quantitative trait loci (QTL) that were shown to strongly influence baseline HbF levels (Thein *et al*, 2009). Seven subjects were homozygous for the IVS I-6 (C-T) β+ thalassemia mutation and only 3 were heterozygous for a favourable genetic modifier.

This study demonstrates that HQK-1001 at 20 mg/kg/day for 24 weeks was well tolerated, significantly increased HbF, and modestly increased total haemoglobin. An interim analysis of a recently completed study of HQK-1001 at 20 mg/kg/day for 26 weeks in 10 patients

with Hb E-β-thalassaemia showed higher mean increase in HbF of 10% (range 4.3–20.9%), with an increase in total haemoglobin > 5 g/l in 3 subjects (Fuchareon *et al*, 2012). These patients all had a β^{O}–thalassaemia mutation, and 9 had at least one favorable allele for the Xmn-I QTL, which is linked to the *HBB*:c.79G>A(β^{E} globin) gene in that population. Three trials have now demonstrated that HQK-1001 increases HbF in β-thalassaemia. It remains to be determined whether the magnitude of increase in HbF is sufficient to reduce long-term complications of chronic haemolysis, ineffective erythropoiesis, anaemia, and transfusion requirements. Further studies of genetically characterized patients for longer periods appear warranted.

Acknowledgments

Funding for this study was provided by a research grant from HemaQuest Pharmaceuticals and by the Georges N. Khoriaty Foundation. SP and DC were supported by NIH grant R01-DK-52962. ClinServ International monitored the study. AGCT Inc. performed the analysis of the Xmn-I polymorphism. Cloret Carl assisted in the manuscript preparation.

References

Bauer DE, Kamran SC, Orkin SH. Reawakening fetal hemoglobin: prospects for new therapies for the β-globin disorders. Blood. 2012; 120:2945–2953. [PubMed: 22904296]

Capellini MD, Graziadei G, Ciceri L, Comino A, Bianchi P, Porcella A, Fiorelli G. Oral isobutyramide therapy in patients with thalassemia intermedia: Results of a Phase II open study. Blood Cells, Molecules, and Diseases. 2000; 26:105–111.

Collins HA, Pearson HA, Giardina P, McDonagh KT, Brusilow SW, Dover GJ. Oral sodium phenylbutyrate therapy in homozygous β-thalassemia: A clinical trial. Blood. 1995; 85:43–49. [PubMed: 7528572]

Fuchareon S, Inati A, Siritanaratku N, Thein SL, Wargin WC, Koussa S, Taher A, Chaneiam N, Boosalis M, Berenson R, Perrine SP. A randomized phase I/II trial of HQK-1001, an oral fetal globin gene inducer, in β-thalassaemia intermedia and HbE/β-thalassaemia. British Journal of Haematology. 2013; 161:587–93. [PubMed: 23530969]

Mankindy R, Faller DV, Mabaera R, Lowrey CH, Boosalis MS, White GL, Castaneda SA, Perrine SP. Short-chain fatty acids induce γ-globin gene expression by displacement of aHDAC3-NCoR repressor complex. Blood. 2006; 108:3179–3186. [PubMed: 16849648]

Musallam KM, Taher AT, Cappellini MD, Sankaran VG. Clinical experience with fetal hemoglobin induction therapy in patients with β-thalassemia. Blood. 2013; 121:2199–2212. [PubMed: 23315167]

Pace BS, White GL, Dover GJ, Boosalis MS, Faller DV, Perrine SP. Short-chain fatty acid derivatives induce fetal globin expressionand erythropoiesis in vivo. Blood. 2002; 100:4640–4648. [PubMed: 12393583]

Perrine SP, Ginder GD, Faller DV, Dover GH, Ikuta T, Witowska HE, Cai SP, Vichinsky EP, Olivieri NF. A short-term trial of butyrate to stimulate fetal-globin gene expression in the beta-globin disorders. New England Journal of Medicine. 1993; 328:81–86. [PubMed: 7677966]

Thein SL, Menzel S, Lathrop M, Garner C. Control of foetal haemoglobin: new insights emerging from genomics and clinical implications. Human Molecular Genetics. 2009; 18(R2):R216–223. [PubMed: 19808799]

Weatherall DJ. The inherited diseases of hemoglobin are an emerging global health burden. Blood. 2010; 115:4331–4336. [PubMed: 20233970]

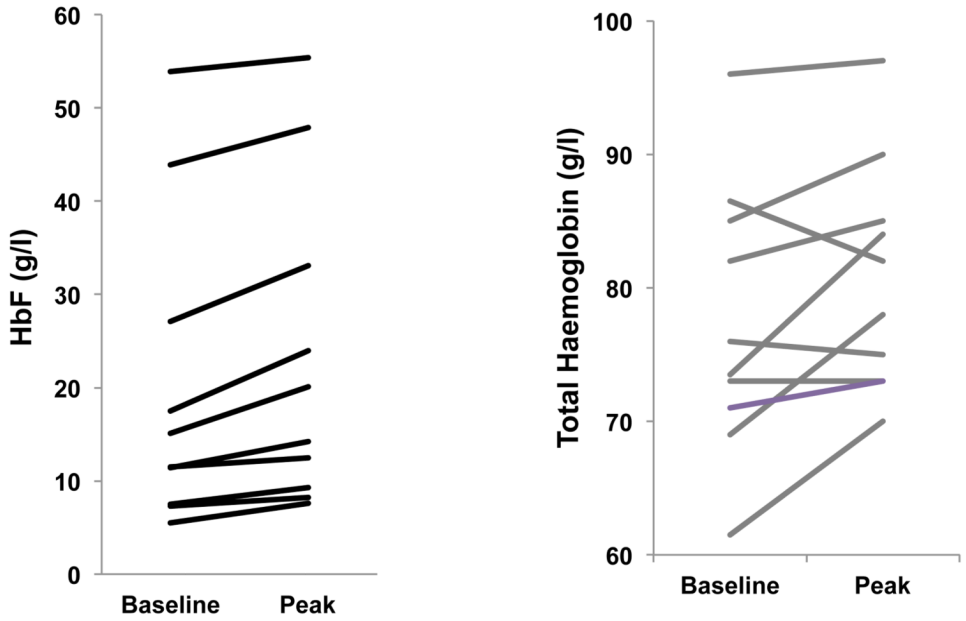

Figure 1. Baseline and peak values for HbF and total haemoglobin

Br J Haematol. Author manuscript; available in PMC 2015 February 01.

Table I

Baseline Characteristics

Subject ID	Age (Years)	Baseline HbF %	Thalassaemia Mutations	HMIP* Rs9399137	*BCL11A* Rs766432	*HBG2*Xmn-1 Rs7482144
001	23	20	IVS I-6/IVS I-6 (T>C)	(N/N)	(N/+)	(N/N)
002	39	7.9	IVS I-6/IVS I-6 (T>-C)	(N/N)	(N/N)	(N/N)
003	32	20	IVS I-110 G>A, IVS II-1G>A	(N/N)	(+/+)	(N/+)
004	21	58	IVS I-6/IVS I-110	(N/N)	(N/+)	(N/N)
005	36	25	IVS I-6/IVS I-6 (T>C)	(N/+)	(N/N)	(N/N)
008	25	20	IVS I-6/IVS I-6	(N/N)	(N/N)	(N/N)
009	52	17	(T>C)CD29/CD29	(N/+)	(N/N)	(N/N)
011	27	9.8	IVS I-6/IVS I-6 (T>C)	(N/N)	(N/N)	(N/N)
012	25	15	IVS I-6/IVS I-6 (T>-C)	(N/+)	(N/N)	(N/N)
013	18	54	IVS I-6/IVS I-6 (T>-C)	(N/+)	(N/N)	(N/N)

For rs9399137, N designates the major allele, T; + designates the minor allele, C.

For rs 766432, N designates the major allele, A; + designates the minor allele, C.

*HMIP = *HBS1L–MYB* intergenic polymorphism.