refixia®▼
nonacog beta pegol

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This Novo Nordisk advertisement is intended for UK Healthcare Professionals

TAKE LIFE ON

Refixia® ONCE-WEEKLY PROPHYLAXIS,[1] GIVING YOUR PATIENTS THE CONFIDENCE TO LIVE BEYOND HAEMOPHILIA B[2-4]

With Refixia® prophylaxis, adolescents (12 years and above) and adults spent approximately 80% of the week with FIX activity levels in the non-haemophilia range (FIX activity higher than 40%)*[2]

EHL Comparison Video
Click here to view on the Refixia UK website

Leopoldo, 61 years old, is an IT engineer and loves spending time sailing. Leopoldo lives with haemophilia B.

Prescribing Information

Refixia®▼ Refixia® 500 IU Refixia® 1000 IU Refixia® 2000 IU (Powder and solvent for solution for injection) Nonacog beta pegol. Nonacog beta pegol is recombinant human factor IX, produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology, covalently conjugated to a 40 kDa polyethylene-glycol (PEG). Refixia® contains approximately 125 IU/ml, 250 IU/ml and 500 IU/ml after reconstitution. **Indication:** Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia B (congenital factor IX deficiency). **Posology and administration:** Prophylaxis: 40 IU/kg body weight once weekly. Adjustments of doses and administration intervals may be considered based on achieved FIX levels and individual bleeding tendency. Patients on prophylaxis who forget a dose are advised to take their dose upon discovery and thereafter continue with the usual once weekly dosing schedule. A double dose should be avoided. On demand treatment: Dose and duration of the substitution therapy depend on the location and severity of the bleeding. Early haemarthrosis, muscle bleeding or oral bleeding / more extensive haemarthrosis, muscle bleeding or haematoma: recommended dose of 40 IU/kg of Refixia - single dose is recommended to treat bleeding. Severe or life threatening haemorrhages: recommended dose of 80 IU/kg of Refixia - additional doses of 40 IU/kg can be given. Surgery: Minor surgery including tooth extraction: recommended dose of 40 IU/kg body weight - additional doses can be given if needed. Major surgery: 1) recommended dose of 80 IU/kg body weight - pre-operative dose. 2) recommended dose of 40 IU/kg body weight - consider two repeated doses of 40 IU/kg (in 1–3 day intervals) within the first week after surgery. Due to the long half-life of Refixia, the frequency of dosing in the post-surgical period may be extended to once weekly after the first week until bleeding stops and healing is achieved. *Intravenous use.* Intravenous bolus injection over several minutes after reconstitution of the powder for injection with the histidine solvent. The rate of administration should be determined by the patient's comfort level up to a maximum injection rate of 4 ml/min. **Contraindications:** Hypersensitivity to the active substance, or to any of the excipients, or to hamster protein. **Special warnings and precautions for use:** Hypersensitivity Allergic type hypersensitivity reactions are possible with Refixia. The product contains traces of hamster proteins. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. In case of shock, standard medical treatment for shock should be implemented. Inhibitors After repeated treatment with human coagulation factor IX (rDNA) products, patients should be monitored for the development of neutralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing. There have been reports in the literature showing a correlation between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with factor IX. Because of the risk of allergic reactions with factor IX products, the initial administrations of factor IX should, according to the treating physician's judgement, be performed under medical observation where proper medical care for allergic reactions could be provided. In case of residual FIX activity levels, there is a risk of interference when performing the Nijmegen modified Bethesda assay for inhibitor testing. Therefore a pre-heating step or a wash-out is recommended in order to ensure detection of low-titre inhibitors. Thromboembolism: Because of the potential risk of thrombotic complications, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing when administering this product to patients with liver disease, to patients post-operatively, to new-born infants, or to patients at risk of thrombotic phenomena or DIC. In each of these situations, the benefit of treatment with Refixia should be weighed against the risk of these complications. Cardiovascular event In patients with existing cardiovascular risk factors, substitution therapy with FIX may increase the cardiovascular risk. Catheter-related complications If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered. Paediatric population Refixia is not indicated for use in children (below 12 years). The listed warnings and precautions apply both to adults and adolescents (12–18 years). Sodium content This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. it is essentially "sodium-free". **Fertility, pregnancy and lactation:** Animal reproduction studies have not been conducted with factor IX. Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during pregnancy and breastfeeding is not available. Therefore, factor IX should be used during pregnancy and lactation only if clearly indicated. **Undesirable effects:** Common (≥ 1/100 to < 1/10): nausea, pruritus (terms pruritus and ear pruritus), fatigue, injection site reactions (injection site pain, infusion site pain, injection site swelling, injection site erythema and injection site rash). Uncommon (≥ 1/1,000 to < 1/100): hypersensitivity, palpitations, hot flush. Unknown (cannot be estimated from the available data): anaphylaxis, inhibitors. Hypersensitivity or allergic reactions have been observed rarely with recombinant factor IX products and may progress to severe anaphylaxis (including shock). In some cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors. Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction. The Summary of Product Characteristics should be consulted for a full list of adverse reactions.

MA numbers and Basic NHS Price:

Refixia® 500 IU	EU/1/17/1193/001	£1,221.50
Refixia® 1000 IU	EU/1/17/1193/002	£2,443.00
Refixia® 2000 IU	EU/1/17/1193/003	£4,886.00

Legal category: POM.

For full prescribing information, please refer to the Summary of Product Characteristics which is available: Novo Nordisk Limited, 3 City Place, Beehive Ring Road, Gatwick, West Sussex, RH6 0PA. **Marketing Authorisation Holder:** Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark. **Date last revised:** July 2018.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Novo Nordisk Limited (Telephone Novo Nordisk Customer Care Centre 0845 6005055).
Calls may be monitored for training purposes.

* Adolescents and adults with haemophilia B treated once weekly with Refixia® 40 IU/kg are predicted to have a FIX activity higher than 40% for 130 hours out of 168 hours, equal to approximately 80% of the week.[2]

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1. Refixia® Summary of Product Characteristics.
2. Tiede A et al. Haemophilia 2017;23(4):547-555.
3. Negrier C et al. Haemophilia 2016; 22 (4): 507-513.
4. Collins PW et al. Blood 2014; 214 (26): 3880-3886

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Acute lymphoblastic leukaemia (ALL) things come to those who wait: 60 years of progress in the treatment of adult ALL

Adele K. Fielding[1] and **Anthony H. Goldstone**[2]
[1]*University College London (UCL) Cancer Institute, and* [2]*HCA Healthcare, Macmillan Cancer Centre, London, UK*

Summary

The UK has made a well-recognised contribution to the international effort to understand and treat acute lymphoblastic leukaemia (ALL) in adults. Work done in the UK by numerous personnel over many years has been instrumental in developing novel risk stratifications, evaluating treatment strategies for adult patients with *de novo* and relapsed disease and in making novel scientific contributions. The UK has championed and achieved very high levels of recruitment to clinical trials and, in particular, is known for success in large, investigator-initiated randomised controlled trials. This historical review charts the progress of clinical research in adult ALL from its inception to the present day.

Keywords: adult, acute lymphoblastic leukaemia, TRIALS.

In the beginning

In 1957, the Medical Research Council (MRC) set up a steering committee to evaluate different forms of treatment in cancer. The first 'Working Party', which included Dr (later Sir) Richard Doll, set up a factorial trial to elucidate the efficacy of mercaptopurine and different doses of corticosteroids in acute leukaemias of both myeloid and lymphoid origin, which showed that adult leukaemia was typically a rapidly fatal disease that was not greatly influenced by those methods of treatment.[1] Trials in acute lymphoblastic leukaemia (ALL), in particular, began in earnest in the early 1970s and continued to be developed by MRC 'Working Parties'. For some years, the MRC 'brand' of trials was internationally respected, being synonymous with high-quality leukaemia trials from the UK. The early studies, of course, long preceded the requirement for a trial sponsor, but were administered by the Clinical Trial Service Unit (CTSU) and Epidemiological Studies Unit at Oxford, an intellectual powerhouse of statistical and trial design expertise, with input from relevant physicians. Up until the 1970s, haematologists were generally trained as pathologists, but a change in emphasis was required as it became increasingly possible to treat diseases such as leukaemia. Anthony (Tony) H. Goldstone exemplified this new breed of professional, having trained in general medicine and haematology in Edinburgh and Cambridge, as opposed to training in 'pathology'. He was appointed to a consultant haematology post at University College London Hospitals (UCLH) in 1976, by the departmental lead Professor Tom Prankerd, a 'physician haematologist' within the Department of Medicine, who underscored the importance of haematologists as general physicians and had been visionary in establishing a separate department of clinical haematology. In a key opinion piece for *The Lancet*, Prankerd made clear that 'interests (of the patient) can be adequately served only by providing a cadre of haematological physicians – doctors who should have a wide background of general medical training as well as a special interest in blood disease.'[2] Along with Tony, Alan Burnett, H. Grant Prentice, Ian Franklin, and I. Jill Durrant were key 'haematological physicians' working on the MRC trials for Adult ALL. Susan M. Richards, Senior Research Fellow at CTSU was a critical statistical and intellectual contributor to both adult and childhood ALL trials, working alongside her colleague Georgina Buck, medical statistician.

You don't always get what you want

During the MRC trials II–VII, various aspects of the basic treatment protocols for ALL were tested with generally disappointing results. Of 1470 children recruited between 1972 and 1979, <50% remained in remission at 4 years.[3] The protocols of the Bayern-Frankfurt-Munster (BFM) West German group then began to be adopted for childhood use. It is hard to imagine nowadays, but blood products were not always readily available, rational use of antibiotics was often absent and expertise amongst nurses and doctors across different centres was variable, meaning that it was hard to control the morbidity and mortality of the intensified therapies. By the 1990s, survival in adult ALL had increased in 5-year disease-free survival from 5% to 38%.[4] The main contribution of these trials so far, had been 'in examining prognostic features in all patients and finding that age and the presence of the Ph chromosome, independent of WBC count, gender, and cell type', were the main features for predicting outcome.

Correspondence: Adele K. Fielding, UCL Cancer Institute, 72 Huntley St, London WC1E 6DD, UK.
E-mail: a.fielding@ucl.ac.uk

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The trials had generally included a treatment approach for both children and adults, but the approaches were managed by separate groups who did not meet together regularly. The childhood–adult age divide had been set at 15 years. The UK community strongly supported randomised trials with the potential to change practice, which has generally been a well-justified approach.

Please will you sponsor me?

The 12th MRC Adult ALL study UKALLX11/ECOG2993, opened in 1993 and was arguably the first UK adult ALL trial of the 'current' era. Even though UKALL10 had been designed as an intensified protocol for adults,[5] this was a step change from UKALL10 in intensity and was the first trial to employ the sort of modified BFM-type regimen that would be recognisable to today's generation. At the time the UKALL12 pilot study was being evaluated, Adele Fielding was a postgraduate medical trainee at UCLH and, being familiar with UKALL10 protocol, recalls being shocked at the intensity of the UKALL12 therapy being given. Individual patients from that era are still fresh in mind, who can forget seeing their case of cerebral venous sinus thrombosis or their first time negotiating with a young patient who is poignantly begging to be allowed home for the weekend? These experiences kindled a long-term desire to facilitate a move from successful but toxic ALL therapy to just successful ALL therapy.

The UKALL12/E2993 was pivotal in several ways. First, it was designed to ask important questions on the relative merits of autologous and allogeneic transplantation, both modalities that were in common use based largely on single-centre reports, each with their adherents and detractors, but with only a modest dataset underpinning their use. Humphrey Kay, who had served as secretary to the MRC's Leukaemia Committee since its founding in 1968 had been instrumental in requesting of Tony Goldstone that these therapies were evaluated. Second, molecular studies of minimal residual disease (MRD) in adults, led by Letizia Foroni[6] were included for the first time in the UK, which also led to the first specimen collection. Third, and critical as an example of the benefits of large international co-operations, this trial was an international collaboration with the Eastern Cooperative Oncology Group (ECOG) of the USA, brokered by Tony Goldstone and Jacob Rowe during a walk in the Black Forest. Jacob Rowe led the ECOG effort with vital contributions from Mary Tallman, Hillard Lazarus, Mark Litzow and Selina Luger, with Elisabeth Paietta co-ordinating the USA central laboratory effort. This transatlantic co-operation was important in a more general sense, helping to bring attention from the USA to the ALL studies being done in Europe and *vice versa*, another distinguishing feature of UKALL12 was that it was already well advanced by the time a Sponsor became a legal requirement. The prodigious outputs from this trial, which was the largest ever trial in adult ALL, are well-known in the community and include seminal papers on the superiority of chemotherapy over autologous transplant[7] and the first cytogenetic risk classification of adult ALL, led by Anthony Moorman.[8] What is less well known about UKALL12 is how hard it was to find a suitable UK sponsor for the trial. As the CTSU Oxford did not offer trial sponsorship, Adele Fielding took up the mantle to persuade her employer University College London (UCL) to sponsor this study, having joined with Tony Goldstone to work on ALL after returning to the UK from a stint working at the Mayo Clinic. UCL eventually agreed to take over sponsorship from Tony Goldstone who was personally sponsoring the study. This, surprisingly, was legal at that time, but not ideal. Following the first Medicines and Healthcare Products Regulatory Agency (MHRA) inspection at UCL where UKALL12 was one of the trials chosen, UCL concluded that UKALL12 that had been carefully conducted and well run under the old regulations was a huge challenge to manage under the new more stringent regulations, underlining the huge changes in trial conduct that had been wrought by the European Union (EU) Directive converted into UK law as The Medicines for Human Use (Clinical Trial) Regulations of 2004. It remains very challenging for all parties to adhere to the directive when studying diseases where therapy is long and complex. The issue of adverse event reporting has been examined in detail in a commissioned report from an international panel of clinicians, clinical investigators, methodologists and regulators should the reader wish to delve further into the concerns and potential solutions.[9]

To date, UKALL12 has contributed to 53 publications. UCL has thankfully agreed to retain sponsorship of UK ALL trials and has also taken on the paediatric trials. Amy Kirkwood has supported the statistical handover from Oxford to London and UK adult ALL trials continue to benefit from her first-class input. The contributions and support of critical trial personnel also cannot be underestimated, we are grateful to numerous staff at CRUK and UCL Cancer Trial Centre for their enormous contribution to adult ALL trials in the UK.

Treat me like a child

During the conduct of UKALL12 it became increasingly clear that teenagers and young adults benefitted from being treated in a more intensive manner than hitherto; a pivotal UK paper showed a much superior outcome for patients aged 15–17 years who had been treated on the paediatric rather than the adult protocol, which at the time had overlapping age limits.[10] The UKALL12 trial management team met together with paediatric trialists in particular, Nick Goulden and Ajay Vora, to agree a revised age limit for our protocols. In a cautious manner, we revised upwards from 18 to 20 years and eventually settled, for pragmatic reasons related to teenage and young adult units, on 24 years as the cut-off for childhood/adult trial enrolment. The UK National Cancer Research Institute (NCRI) Adult ALL group created a

specialist teenage and young adult team of Clare Rowntree and Rachael Hough, who worked across the NCRI paediatric and adult groups to guide and assist in the adoption of the paediatric protocols in the adult-care setting. The increasing understanding that there would not be one correct treatment for all patients with ALL, rather, alternative approaches for patients of different ages would be required, set the direction for the UK to extend its efforts to patients at the other end of the age spectrum who had largely been excluded from clinical trials. This had long been a topic of importance promoted by Steve Proctor. UKALL60+ became the first ever UK ALL study open to older patients with no upper age limit.

Is there anything there?

Monitoring of MRD in ALL allows precise quantification of small amounts of disease that cannot be detected by standard approaches. Although this can be done by flow cytometry, the detection and monitoring of patient-specific immunoglobulin heavy chain/T-cell receptor re-arrangements is the most standardised approach due to the vision and persistence of founding chair Jacques Van Dongen who began the European Study Group on MRD detection in ALL, which we now know as EuroMRD. Multiple laboratories from 25 countries across Europe, Asia, Australia, North and South America participate in a twice annual quality-control programme twice per year, contribute to the development of guidelines for the interpretation of real-time quantitative-polymerase chain reaction (RQ-PCR)-based MRD data[11] and collaborate on development and evaluation of new MRD strategies and techniques. Adult ALL in the UK has benefitted enormously from this co-operation. MRD has been incorporated into clinical decision-making and treatment stratification in trials and is now funded by the UK National Health Service (NHS) and carried out as standard of care, strictly according to EuroMRD guidelines. The UK NCRI Adult ALL group and Adele Fielding in particular, are very grateful for the support of the Tapner family, whose substantial donation enabled the creation of the national adult ALL MRD laboratory and the transition of MRD in adult ALL from a research-funded test to a test adopted and funded by the NHS. Based on its potential to eliminate MRD,[12] regulatory approval and UK reimbursement of the novel immunotherapy agent, blinatumomab was agreed in 2019.

What doesn't kill me makes me stronger

The UK has made a particular contribution to the study of bone marrow transplant in ALL. The results from the pioneering 'donor *versus* no-donor' analysis of the outcome of allogeneic stem cell transplant in UKALL12 showed that patients with high-risk ALL did not benefit from allograft, although there was a benefit for those with standard-risk ALL. This counterintuitive finding resulted from a treatment-related mortality that equalled the considerable reduction in relapse risk. The main contributor to the excess toxicity in the high-risk group was age,[13] suggesting that if the immunotherapeutic benefit of allograft were to be realised in older persons, an alternative, less toxic approach was needed, leading to the incorporation of the largest ever prospective study of a reduced intensity-conditioned (RIC) approach in adult ALL in the UKALL14 study. David Marks has been pivotal to the effort of studying RIC allogeneic stem cell transplant in UKALL14 and has already established the follow-on study, ALL-RIC study. We are also fortunate to have important additional immunotherapy approaches either approved for adults with persistent or relapsed disease, namely blinatumomab or chimeric antigen receptor T (CART) cells, which are showing strong potential for safe and effective therapy of adult ALL in early phase clinical trials. The work of Martin Pule, Claire Roddie and Karl Peggs, based at UCL, has been critical to the UK-specific effort in that regard. The emergence of numerous genetic subgroups of ALL, alongside a plethora of targeted therapies, now generates wonderful opportunities for novel trial designs, but at the same time challenges the feasibility of the academically-initiated large randomised controlled trials in defining the role of these agents.

What shall we do next?

Nowadays, ALL trials are developed via the NCRI ALL subgroup and compete for external peer-reviewed funding. We are grateful to CRUK, which has been a major funder of these sorts of clinical trials. We also have been grateful, both then and now, for the resources of the NHS, which provides the vital trial infrastructure 'on the ground' and makes large investigator-initiated trials relatively inexpensive to conduct by comparison with pharma studies. We have always been fortunate to co-operate with informed and enthusiastic local Principal Investigators in NHS centres, who are the vital backbone of ALL trial success. Numerous investigators have also stepped up to perform outstanding roles in recruiting patients, participating in trial management groups, sharing expertise on the NCRI Adult ALL group and participating in the processes of novel agent approval, Tobias Menne, Nick Morley, Andrew McMillan and Debby Yallop among them. The UK has been prescient in recognising and promoting trial entry to patients with rare diseases such as ALL as the standard approach. To that end, we in the UK have typically designed our later phase trials without stringent exclusion criteria, facilitating recruitment of 80–90% of the incident population, thus ensuring that our trial data has pragmatic, real-life relevance. Another important aspect of UK NCRI-developed trials is the critical role of patient and public engagement; the group is extremely fortunate to work with Gill Murphy in this regard.

We have completed the UKALL60+, the first ever trial designed specifically for older adults with ALL, a significantly underserved group who had largely been neglected in the

trial arena. The UKALL14 has also been completed and whilst the clinical data are being prepared for publication, the first adult ALL biobank is providing valuable material for correlative science. Younger investigators are becoming interested not just in the clinical management of ALL, but in understanding the molecular and cellular biology of the disease and developing trials which are age-appropriate and incorporate correlative science. Richard Burt, Anna Castleton, Kate Bailey and Bela Patel who have passed through the Fielding laboratory and retained an interest in ALL have all made important scientific contributions in understanding the contribution of the stromal microenvironment,[14,15] CD20 expression, MRD and leukaemia-initiating cells.[16,17] Drs Burt and Patel had the specific financial help and encouragement of their academic 'grandfather', Tony Goldstone, underscoring the critical importance of realising that progress is typically made by 'standing on the shoulders of giants'.

The ALL work in the UK has hugely benefitted not only from UK-derived mentorship, but from the co-operation with and learning from other national groups and major figures. The publications and international profile of the UK group show how much we gained from working with the United States ECOG. We have also enjoyed a 'harmonious' and beneficial collaboration with numerous European colleagues through the European Working Group on ALL (EWALL) founded some years ago by Dieter Hoelzer and Robin Foa, a forum for co-operation and exchange of ideas. Adele Fielding is particularly grateful to be the current rotating chair of this group and still belong to European initiatives. The EWALL has led directly to some ongoing co-operative projects and will foster some excellent large data science within the EU-based Healthcare Alliance for Resourceful Medicine Offensive against Neoplasms (HARMONY).

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