# Long-Term Safety and Efficacy of Autologous HSC–Gene Therapy for ADA-SCID

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**Abstract**

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**Background**

Severe combined immunodeficiency due to adenosine deaminase (ADA) deficiency (ADA-SCID) is a life-threatening inborn error of immunity for which lentiviral gene therapy has been investigated in clinical trials.

**Methods**

We treated 62 patients with ADA-SCID in the U.S. and U.K. between 2012-2019 with busulfan non-myeloablative conditioning followed by transplantation with autologous CD34+ hematopoietic stem cells transduced ex vivo with a lentiviral vector encoding human *ADA*. Here we report the long-term results from this cohort representing 474 years of patient follow-up with a median follow-up of 7.5 years.

**Results**

Overall survival was 100% and 95% (59/62) event-free survival (defined as absence of rescue allogeneic hematopoietic stem cell transplantation, re-initiation of enzyme replacement therapy, or additional gene therapy). All 59 patients who achieved successful gene-marked engraftment at 6 months have remained off enzyme replacement therapy while maintaining stable gene-marking, ADA enzyme activity, metabolic detoxification, and immune reconstitution through last follow-up. 58/59 (98%) of these patients successfully discontinued IgG replacement therapy with evidence of robust response to vaccinations. No patients experienced a leukoproliferative event or clonal expansion.

**Conclusions**

These long-term findings demonstrate the sustained clinical efficacy and safety of lentiviral gene therapy for ADA-SCID, representing a curative treatment. These data represent the largest patient cohort supporting the durability and safety of autologous CD34+ haematopoietic stem cell lentiviral gene therapy. (Funded by the National Heart, Lung, and Blood Institute, and others. ClinicalTrials.gov NCT04049084)

**Introduction**

Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID) is an ultra-rare genetic disease that results in the accumulation of toxic adenine metabolites that severely impair lymphocyte development [1]. Patients have profound lymphopenia leaving them susceptible to life-threatening infections; without treatment life expectancy is 2 years or less[2]. Non-immunological features of the disease, including sensorineural deafness, developmental delay, behavioural challenges and urogenital abnormalities, are variable but common and not improved by treatment[3,4].

The main therapeutic interventions for ADA-SCID are ADA enzyme-replacement therapy (ERT) and allogeneic hematopoietic stem-cell transplantation (HSCT). ERT with pegylated ADA enables systemic metabolic detoxification resulting in partial immune reconstitution. However, incomplete immune reconstitution is associated with progressive long-term mortality due to breakthrough opportunistic infections, autoimmunity and malignancy[6,7]. Therefore, current guidelines recommend ERT as a stabilizing measure prior to definitive treatment with allogeneic HSCT or autologous gene therapy[5]. Allogeneic HSCT outcomes for ADA-SCID have improved over the past 20 years, with overall survival (OS) >85% and event-free survival (EFS) >70%[7-10]. Widespread adoption of newborn screening programs for SCID has contributed to this improvement, with early identification of patients allowing transplantation in the absence of active infection[11]. However, alloreactivity still leads to HSCT-related complications, with graft-versus-host disease (GvHD) remaining a significant source of morbidity and, rarely, mortality.

Ex vivo autologous HSC gene therapy has emerged as a safe and effective therapeutic approach for ADA-SCID, and obviates risks associated with alloreactivity and immune suppression. Gammaretroviral-mediated gene therapy has shown long-term efficacy for ADA-SCID, but insertional oncogenesis remains a risk, with T- cell leukaemia reported in one patient[12]. In contrast to gammaretroviral vectors, third-generation self-inactivating lentiviral vectors have been engineered for improved safety by removal of transforming elements in the viral long terminal repeats (part of the lentivirus genome) to avoid transactivation of oncogenes[13]. We therefore

developed a self-inactivating lentiviral vector, EFS-ADA-LV, and tested it in the treatment of children with ADA-SCID in non-randomised, open-label, phase I/II clinical studies in the US and UK (NCT01852071, NCT02999984, NCT01380990, NCT03765632). We have previously reported the initial results of these trials with 24–36-month follow-up of 50 pediatric ADA-SCID patients, demonstrating 100% overall survival and >95% EFS[14]. Here, we report comprehensive long-term follow-up efficacy and safety data for 62 patients with a minimum of 5-years follow-up after gene therapy (median 7.5 years, 474 patient years follow-up).

**METHODS**

*Study design*

After completing short-term follow-up studies,[14] patients were enrolled in the current study, which was designed to extend patient-monitoring to ensure a total duration of 15 years, in compliance with regulatory requirements[15-17]. Eligibility criteria for enrolment in this study included prior treatment with an autologous *ex vivo* EFS-ADA lentiviral gene therapy product and evidence of persistent, detectable gene marking at completion of treatment trial (defined as VCN ≥0.001 in PBMC), as described in the protocol, which can be found at nejm.org. There were no exclusion criteria. For the purposes of the current report the evaluable patients were those who had completed at least 5 years of follow-up. Patients in the United States were treated and followed at the University of California, Los Angeles, and the National Institutes of Health. In the United Kingdom, patients received treatment and monitoring at Great Ormond Street Hospital NHS Foundation Trust, in London. Orchard Therapeutics designed the study; DBK, CB, KM and KV collected and analysed data, DBK and CB vouch for the data analysis. CB wrote the first draft of the manuscript; DBK, KM and KV edited; all authors reviewed the manuscript and CB/DBK decided to publish the paper.

*Clinical Follow-up*

Patients attended for scheduled follow-up visits for evaluation every 6 months from Year 3 to 5 post- gene therapy, and annually thereafter until the end of the 15-year follow-up period. Each evaluation included a comprehensive clinical history assessment, with a focus on concomitant medications such as prophylactic

antibiotics, immunoglobulin replacement, ERT, as well as the documentation of adverse events. Physical examinations were conducted alongside essential laboratory investigations, including complete blood counts, serum immunoglobulin levels, lymphocyte subsets, ADA enzyme activity, adenine nucleotides in serum samples and vector copy number (VCN) quantification in blood cells. Vector integration site analyses were performed on genomic DNA extracted from peripheral blood mononuclear cells (PBMCs). Samples for vector integration site analyses and assay of replication-competent lentiviruses were stored annually, with the assay to be performed only when clinically indicated, such as in cases of suspected haematological malignancy or laboratory evidence of clonal expansion (which did not occur). Further methodologic details are described elsewhere.[14]

*Endpoints*

The primary outcomes were long-term safety and efficacy measures. Primary safety endpoints included the incidence and type of delayed serious adverse events, such as hospitalizations, infections, autoimmunity, haematologic disorders, and neurologic complications, along with the long-term safety of gene transfer assessed through analyses of vector-integration sites, and screening for replication-competent lentivirus. Primary efficacy endpoints were overall and event-free survival. An “event” was defined as death, the need for reinstitution of ERT, a rescue allogeneic haematopoietic stem cell transplant, or additional gene therapy. Secondary endpoints included: a) the proportion of patients off immunoglobulin replacement, b) the proportion achieving protective titres to tetanus or pneumococcal vaccines, and c) the proportion who sustained the discontinuation of fungal or viral prophylaxis.

*Statistical analysis*

We used medians with ranges to describe quantitative variables and frequencies for categorical variables. Overall survival and event-free survival were analysed and presented in Kaplan-Meier curves. Data analysis was performed using Stata Statistical Software Version 18 and GraphPad Prism 10.

*Ethics and Approvals*

This study was sponsored by Orchard Therapeutics (Europe) Limited, approved by the appropriate independent ethics committees and institutional review boards, and conducted in compliance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice Guidelines. All patients, or their parents or guardians, provided written informed consent to participate in the study and assent was provided by patients where appropriate.

## RESULTS

### Baseline characteristics

The characteristics of the patients at baseline and drug-product details are reported in Table 1 and Table S1. The cohort comprises 62 ADA-SCID patients treated with gene therapy in the United States (n=33) and United Kingdom (n=29) between 2012 and 2019 and followed for a minimum of 5 years (median 7.5 years, range 5 to 11.2 years). 50 patients were enrolled in clinical studies and 12 were treated through a compassionate-use programme. The median age of treatment was 10.1 months for U.S. patients (range 4.5-51.4 months) and 14 months (range 4 to 194 months) for U.K. patients. Most U.S. patients were identified through newborn screening programmes (70%, 23/33). In the U.K., newborn screening was not in place during recruitment of patients, but 4 patients were identified through family history; the remaining patients presented with features consistent with a diagnosis of SCID including infection, failure to thrive and lymphopenia. The majority of patients had received standard-of care-treatment including enzyme replacement therapy (62/63), prophylactic antimicrobials (63/63) and immunoglobulin replacement therapy (57/62). This patient cohort is representative of ADA-SCID patients in both the US and UK, based on publicly available data and center experience (Table S2). Two patients previously treated in a clinical study in the U.K. had received gammaretroviral HSC gene therapy and had experienced failure of that treatment[18].

Bone marrow was used as a source of hematopoietic progenitors for all U.S. patients, whereas in the U.K study, GCSF- and plerixafor-mobilised PBSCs were used for 90% of products, with the remainder using bone

marrow. Accordingly, the median CD34+ cell dose was higher in the UK cohort relative to the US cohort ($14x10^6$ CD34+ cells/kg vs $7.4x10^6$ CD34+ cells/kg). Of the 33 U.S. patients, 20 received a fresh product, 11 received a cryopreserved product and 2 received a combination of fresh and cryopreserved products. In the U.K., 19 patients received fresh products, 9 received a cryopreserved product, and 1 received a combination of both over consecutive days. The same lot of the lentiviral vector was used at both sites and median vector copy number per cell in the drug product was 3.7 in the US and 2.7 in the U.K. (Table S1). All patients received non-myeloablative conditioning with busulfan prior to infusion of gene-corrected cells. Therapeutic drug monitoring was employed prior to infusion of cryopreserved products, targeting a busulfan area-under-the-concentration versus time curve (AUC) of 20 mg*h/L.

**Efficacy**

In this cohort of 62 patients, at the time of last follow-up, 62 survived (overall survival was 100%); and 59 (95%) survived free of events (Figure 1). EFS was 94% among the patients in the U.S. study and 97% among the patients in the U.K. study. Three patients across both sites experienced early treatment failure characterized by absent or declining gene marking by 6 months post-treatment, 2 of whom were reported previously[14]. All 3 patients remain well. The two U.S. patients received rescue allogeneic HSCT and the U.K. patient is maintained on enzyme replacement therapy and immunoglobulin replacement therapy while awaiting HSCT. Across both sites, efficacy results are similar for patients who received fresh or cryopreserved formulations.

In the 59 patients with successful engraftment, vector gene marking in granulocytes was evident at 3 months post-transplant, with a median granulocyte vector copy number of 0.13 copies per cell in U.S. cohort and 0.32 copies per cell in the U.K. cohort, corresponding to an estimated transduction of ~10 to 30% gene-modified long-term HSCs (Figure 2). Granulocyte gene marking in each cohort has been maintained at stable levels through last follow-up, demonstrating secure engraftment of gene-corrected hematopoietic stem cells.

In PBMCs, which exhibit a selective survival advantage for gene-corrected lymphocytes, median vector copy numbers increased from 0.5 at month 3 to 0.97 at month 24 and have been maintained at stable levels in both cohorts.

In line with the original trial protocol, patients stopped ERT one month after drug product infusion. Of those 59 patients who successfully engrafted gene-modified HSCs, all remain metabolically detoxified as evidenced by an absence of toxic metabolites (Figure S2). ADA enzyme activity in red blood cells in US patients and PBMCs in U.K. patients has remained at stable levels within or above the normal range in all patients.

At the latest follow-up visit, lymphocyte counts of the 59 engrafted patients were maintained within or close to the normal ranges for age, including T-, B- and NK-lymphocyte populations (Figure 2 and Supplemental Figure 3). After the initial post-therapy period of immune recovery and as previously described, CD3+ T-cell counts remained >1000/ul (median 1054/ul in U.S. patients and 1770/ul in U.K patients) throughout the duration of follow-up with CD4+ T cell counts sustained in the normal range (median 622/ul and 940/ul in the U.S. and U.K. cohorts respectively). Importantly, naïve (CD3+) T-cell populations were evident in all 59 patients at appropriate levels (exceeding 1000 cells/ml) (Figure S3) and T-cell-receptor excision circle counts showed a durable increase after treatment, consistent with de novo generation of naïve T-cells up to 11 years post therapy (data not shown). T-cell receptor V$\beta$ repertoire remained diverse throughout follow-up with no concerning clonal expansions. Natural killer cell numbers were also sustained within normal ranges.

Robust CD19+ B-cell reconstitution supported stable immunoglobulin levels over time (Figure 3), allowing 100% of U.K. patients to discontinue immunoglobulin replacement therapy by 37 months post-treatment and 97% of U.S. patients by 43 months. IgM and IgA levels also remained within the normal range (Figure S4A and B). Protective tetanus antibody levels were demonstrated in 100% of vaccinated patients (Figure S4C).

**Safety**

No vector-related safety concerns have been noted in any patient receiving gene-modified HSCs; specifically, no leukoproliferative or myelodysplastic complications, no findings of clinically relevant monoclonal expansions, and no evidence of replication-competent lentivirus were detected in any patient sample. Vector integration site analysis demonstrated no persistent clonal dominance and benign integration profiles were reported in PBMC samples analysed up to 120 months post-infusion. Figure 4 and Figure S5 show the polyclonal nature of vector integration for all engrafted patients, representing the frequency of the 10 most prominent integration sites detected in PBMCs at last available follow-up.

Adverse events occurring within 24 months post-infusion in U.S. patients and 36 months post-infusion in U.K. patients have been previously reported for most patients described here[14]. Adverse events reported in long-term follow up studies were mild to moderate and considered by the investigators to be unrelated to the investigational medical product or the treatment protocol (Table S3). In the U.K. patient cohort, seven serious adverse events were reported more than 3 years after treatment (six infections and one event related to a planned surgical procedure) and none were reported after 5.7 years follow-up. All resolved. There were twelve self-limiting infections among the 33 US subjects occurring within 6 years of treatment, and one urinary tract infection at 9 years post-infusion. Infections were typically self-limited and consistent with routine childhood pathogens but graded as serious adverse events due to precautionary admissions given patients' status as post-transplant former SCID patients.

**Discussion**

In previous studies, we reported that lentiviral gene therapy provided a safe and effective treatment in 50 patients with ADA-SCID, demonstrating 100% overall survival and >95% event free survival up to 36 months post-infusion. The initial procedure was well tolerated with few complications and most patients achieved full immune recovery and sustained metabolic detoxification leading to reduced infection rates and the ability to stop ERT and immunoglobulin replacement therapy. We can now confirm the sustained clinical

benefit and excellent safety profile in a cohort expanded to 62 patients with a median follow-up of 7.5 years and over 10 years follow-up in 5 patients. Gene marking in peripheral blood remains stable over time, and this is reflected in durable lymphocyte counts which remain within normal ranges. Notably, vector copy number in the granulocyte compartment, which is indicative of gene marking in HSC populations, also remained stable. Alongside the robust clinical response and continued generation of naïve T cells, this suggests that long-term repopulating HSC populations were genetically corrected. No treatment failures were recorded beyond the 1-year time point.

The safety profile of this therapy is reassuring. As expected with an autologous product, no patients developed signs of alloreactivity nor the type of complications associated with the prolonged immune suppression required in allogeneic HSCT. Importantly, no persistent clonal expansion was seen in any patient and integration-site analysis confirmed a benign integration profile of the vector in all patients.

HSCT, the current standard of care for ADA-SCID, has improved over the past two decades, with overall survival reaching 90% in one recent large series, even in the context of non–HLA identical donors[7]. Although an unconditioned infusion of HSCs from an HLA-matched related donor is currently the preferred first line treatment[5], long-term results including immunological parameters and metabolic detoxification may be compromised by lack of conditioning to secure engraftment of HSC-repopulating progenitors, with ~25% of patients requiring a second procedure[8]. Non-myeloablative conditioning regimens are increasingly used to support myeloid engraftment, which may allow for sustained immune recovery. Nonetheless, the gene therapy protocol described here involves >70% reduced busulfan exposure which could afford patients less chemotherapy-related toxicities including long-term risks of infertility and secondary malignancies. Additionally, autologous HSCT with gene therapy eliminates any complications related to alloreactivity.

Long-term safety and efficacy data has recently been published for a gammaretroviral (γRV) gene therapy to treat ADA-SCID which is available as a fresh product in Milan (Strimvelis®). 43 patients have been treated

with 100% overall survival and 88% event-free survival (defined in the same terms as reported here)[12]. 19 of those patients received the licensed product of which 6 failed treatment. In line with our results, treatment failure for the γRV occurred relatively early post-therapy with 5 of 6 patients requiring intervention within 2 years and 1 at 4.5 years. T-cell acute lymphoblastic leukemia was reported in one patient 4.7 years after treatment and determined to be directly related to the treatment:[12] the patient's blast cells had a single γRV insertion close to *LMO2*, a proto-oncogene which has been implicated in the development of hematological malignancies in previous γRV gene therapy clinical trials for X-linked SCID[19-21].

In our studies, we utilised a self-inactivating lentiviral vector (SIN-LV) containing a short elongation factor-α (EF-1α) mammalian promoter driving *ADA* transgene expression. Our results add to the expanding safety data available for SIN-LV gene therapy, providing the largest single cohort of treated patients to date. There is emerging evidence that promoter choice may be a relevant factor in insertional oncogenesis, despite the overall safety profile of SIN-LV vectors themselves[22]. In a recent trial of lentiviral gene therapy for X-linked cerebral adrenoleukodystrophy (cALD), 10% of patients developed haematological malignancies with reported insertion sites in *MECOM* and *PRDM16*,[23] genes implicated in insertional oncogenesis in γRV trials in the past[24-26]. Unlike other SIN-LV based gene therapy trials, the cALD trial used a retroviral long-terminal repeat (LTR)-derived *MNDU3* promoter-enhancer element that is capable of transactivating expression of genes external to the integrated LV cassette. To our knowledge, no vector-related adverse events have been reported in clinical trials using lentiviral vectors containing the same EF-1α promoter used in this study.

Despite the durable treatment effect and safety profile we have reported here, this therapy has shown limited commercial viability through traditional commercialisation routes, primarily due to the small market population and high cost of complex drug-product manufacture for individual patients. The cost of the drug-product is high, but overall treatment costs may offer longer-term savings through reduced length of hospital stay, no alloreactive complications or complications related to requisite post-HSCT immune suppression and fewer late effects of chemotherapy due to the reduced dosage used in gene therapy. Both institutions

involved in the development of this programme are actively exploring alternative ways to provide this highly effective treatment to patients with ADA-SCID. This could be achieved via the scalable, platform manufacturing processes, to reduce development costs for subsequent similar products, for the establishment of innovative funding models, which could make these treatments more accessible, and streamlining the regulatory processes for faster approval and commercial availability.

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**FIGURES AND TABLES**

**Figure Legends**

Figure 1. **Kaplan-Meier Curves for Event-free Survival.**
Event-free survival is defined as absence of rescue allogeneic hematopoietic stem cell transplantation, re-initiation of enzyme replacement therapy, or additional gene therapy. Tick marks indicate censored data.

Figure 2**. Median vector gene marking in granulocytes and PBMCs.**
Graphs show median vector copy number (VCN) with standard error of mean plotted against time since infusion of drug product to latest follow up in both granulocytes (left hand panel) and peripheral blood mononuclear cells (PBMCs).

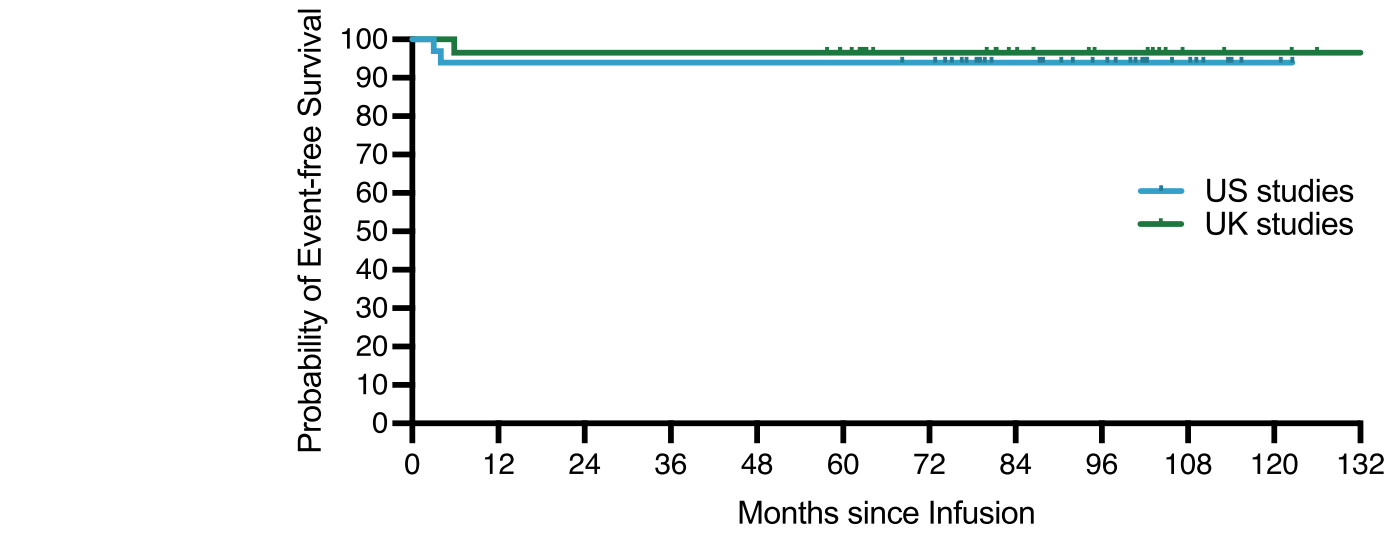
Figure 3. **Median CD3+ T lymphocyte and CD19+ B lymphocyte counts.**
Median absolute CD3+T and CD19+B lymphocyte counts (with standard error of mean) to latest follow up as determined by flow cytometry. Dotted lines represent median normal lymphocyte subset count for ages of patients included in studies.

Figure 4**. Vector integration site analysis.** The coloured stacked bars represent the 10 most frequent integration sites in each sample; the grey area above represents all other detected integration sites. VISA assays were performed at a mean of 73.2 months after drug product infusion (range 24-120 months).

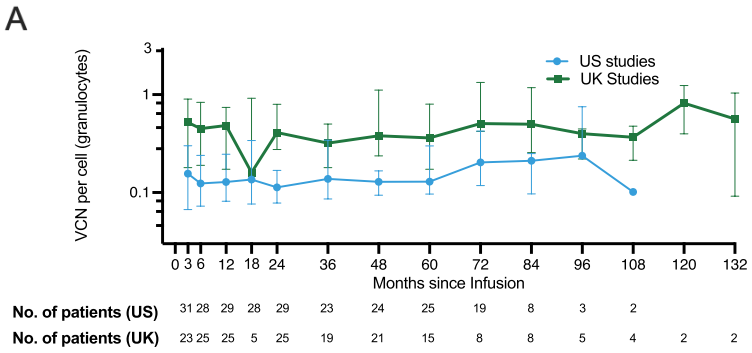
**Table 1. Demographics**

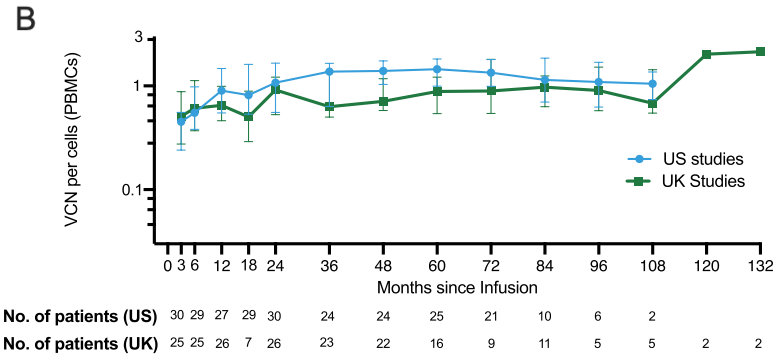
| Demographic characteristics of the patients | U.S. Study | U.K. Study |
|---|---|---|
| **Sex – no. (%)** | | |
| Female | 18 (55) | 13 (45) |
| Male | 15 (45) | 16 (55) |
| **Race – no. (%)*** | | |
| Asian | 0 | 4 (14) |
| Black | 2 (6) | 8 (28) |
| Hispanic | 6 (18) | 1 (3) |
| White | 19 (58) | 16 (55) |
| Other | 5 (15) | 0 (0) |
| Unknown | 1 (3) | 0 (0) |
| **Timeline** | | |
| Median age at diagnosis (range) - months | 1 (0-36) | 3 (0 - 25) |
| Median age at time of treatment (range) - months | 10 (4-51) | 14 (4-194) |
| Median follow-up (range) - years | 8 (5-10) | 7 (5-11) |
| **Trigger for diagnosis¥** | | |
| Newborn screening | 23 (70) | 1 (3) |
| Positive family history | 0 (0) | 4 (14) |
| Parental consanguinity | 0 (0) | 6 (21) |
| Severe, recurrent or persistent infection | 8 (24) | 27 (93) |
| Failure to thrive | 3 (9) | 12 (41) |
| Cytopenias | 2 (6) | 17 (59) |
| **Active infection during GT - no. (%)¥¥** | | |
| Bacterial† | 0 (0) | 7 (24) |
| Fungal | 0 (0) | 0 (0) |
| Viral≠ | 0 (0) | 19 (66) |
| **Type of cells — no. (%)** | | |
| Bone marrow | 33 (100) | 3 (10) |
| Mobilized leukapheresis | 0 (0) | 26 (90) |
| **Formulation** | | |
| Fresh | 19 (58) | 19 (66) |
| Cryopreserved | 12 (36) | 9 (31) |
| Combined (fresh & cryopreserved) | 2 (6) | 1 (3) |
| **No. of products infused (%)** | | |
| 1 | 31 (94) | 28 (97) |
| 2 | 2 (6) | 1 (3) |
| **Median CD34+ cells infused per kg of body weight (range) - x $10^6$** | 7.4 (2.1 -11.4) | 14 (4.5-38.9) |
| **Median Drug-product vector copy-number (range) - copies/cell** | 3.7 (1.56-6.53) | 2.7 (0.5-13.3) |
| **Receipt of busulfan nonmyeloablative conditioning — no. (%)** | 33 (100) | 29 (100) |
| **Median AUC (range) - mg x h/L** | Fresh 16.6 (9.6-16.3)<br>Cryo 19.5 (16.3-21.7) | Fresh 19.2(13.1-30.9)<br>Cryo 22.3 (19.6-45.4) |

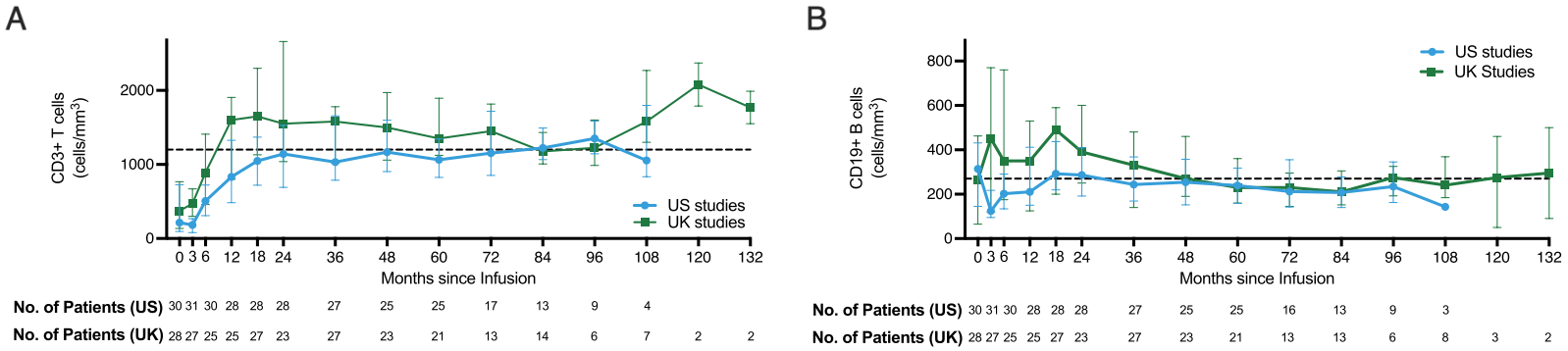
***** *Race and ethnic group were reported by the patients or their guardians;* ¥*Note that patients could have had more than one diagnostic triggers;* ¥¥ *Active infections per patient. Note that each patient could have had more than one active infection;* † *Five patients with BCG disease/exposure on prophylaxis, and one with Clostridium difficile in stool;* ≠ *2 patients with EBV viraemia, 1 with Adenoviraemia and 1 with CMV viraemia, the rest included respiratory viruses (Coronavirus, Rhino/Enterovirus, influenzae, parainfluenza or metapneumovirus on NPA or BAL) and stool viruses (Adenovirus, Norovirus, Rotavirus, Sapovirus). The US trial required treated patients to be free of active infections;* ∞ *Abbreviations: AUC, area under curve; kg, kilogram*.

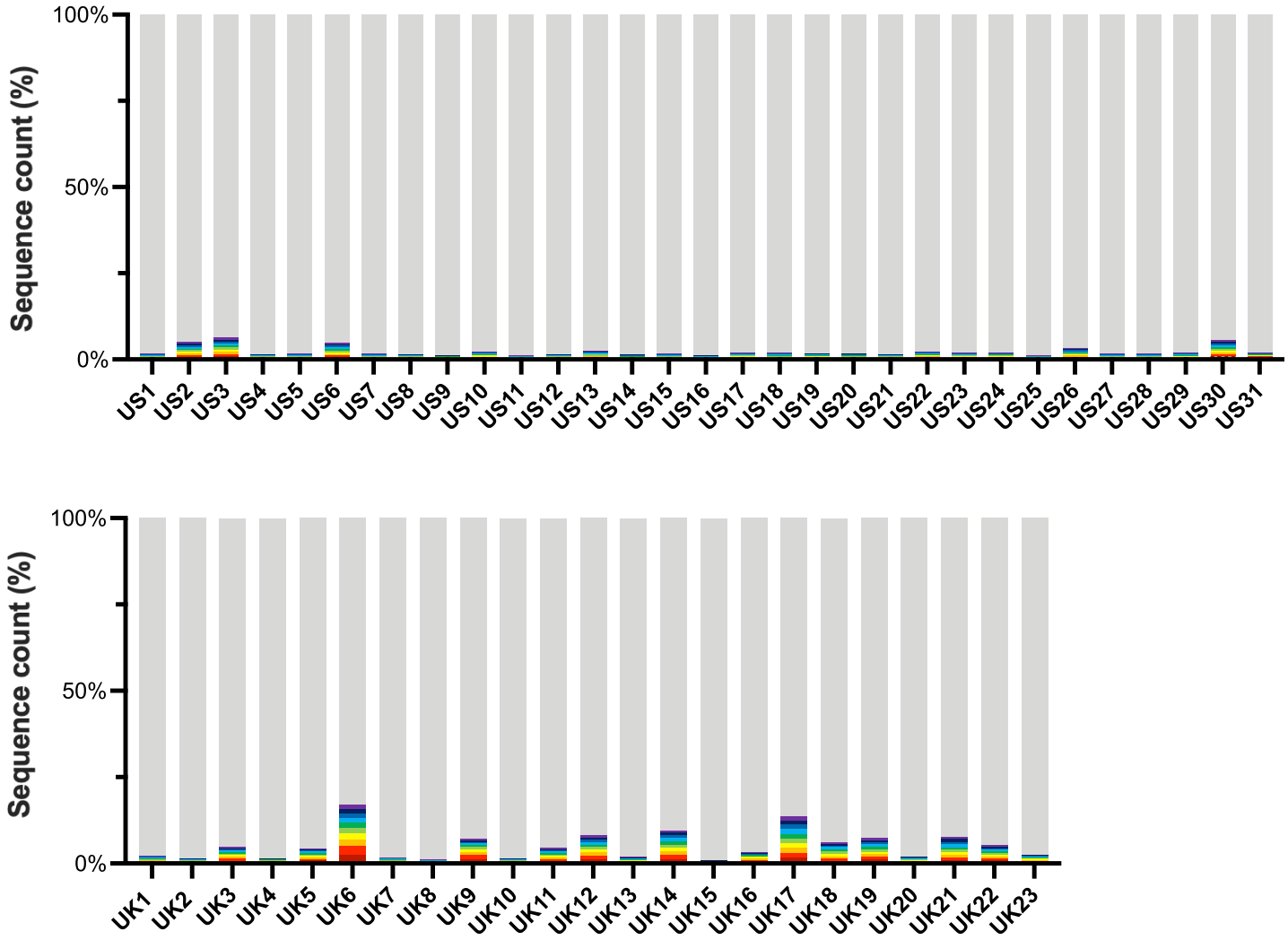



| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number at risk (US) | 33 | 31 | 31 | 31 | 31 | 31 | 30 | 20 | 16 | 8 | 2 | 0 |
| Number at risk (UK) | 29 | 28 | 28 | 28 | 28 | 28 | 19 | 15 | 10 | 5 | 4 | 2 |


A
VCN per cell (granulocytes)
3
1
0.1
US studies
UK Studies
0 3 6 12 18 24 36 48 60 72 84 96 108 120 132
Months since Infusion
No. of patients (US) 31 28 29 28 29 23 24 25 19 8 3 2
No. of patients (UK) 23 25 25 5 25 19 21 15 8 8 5 4 2 2


B
VCN per cells (PBMCs)
3
1
0.1
US studies
UK Studies
0 3 6 12 18 24 36 48 60 72 84 96 108 120 132
Months since Infusion
No. of patients (US) 30 29 27 29 30 24 24 25 21 10 6 2
No. of patients (UK) 25 25 26 7 26 23 22 16 9 11 5 5 2 2


A
CD3+ T cells (cells/mm3)
2000
1000
0
US studies
UK studies
0 3 6 12 18 24 36 48 60 72 84 96 108 120 132
Months since Infusion
No. of Patients (US) 30 31 30 28 28 28 27 25 25 17 13 9 4
No. of Patients (UK) 28 27 25 25 27 23 27 23 21 13 14 6 7 2 2
B
CD19+ B cells (cells/mm3)
800
600
400
200
0
US studies
UK Studies
0 3 6 12 18 24 36 48 60 72 84 96 108 120 132
Months since Infusion
No. of Patients (US) 30 31 30 28 28 28 27 25 25 16 13 9 3
No. of Patients (UK) 28 27 25 25 27 23 27 23 21 13 13 6 8 3 2


Sequence count (%)
100%
50%
0%
US1
US2
US3
US4
US5
US6
US7
US8
US9
US10
US11
US12
US13
US14
US15
US16
US17
US18
US19
US20
US21
US22
US23
US24
US25
US26
US27
US28
US29
US30
US31
Sequence count (%)
100%
50%
0%
UK1
UK2
UK3
UK4
UK5
UK6
UK7
UK8
UK9
UK10
UK11
UK12
UK13
UK14
UK15
UK16
UK17
UK18
UK19
UK20
UK21
UK22
UK23