ORIGINAL ARTICLE

Lentiviral Gene Therapy for Cerebral Adrenoleukodystrophy

F. Eichler, C.N. Duncan, P.L. Musolino, T.C. Lund, A.O. Gupta, S. De Oliveira, A.J. Thrasher, P. Aubourg, J.-S. Kühl, D.J. Loes, H. Amartino, N. Smith, J. Folloni Fernandes, C. Sevin, R. Sankar, S.A. Hussain, P. Gissen, J.-H. Dalle, U. Platzbecker, G.F. Downey, E. McNeil, L. Demopoulos, A.C. Dietz, H.L. Thakar, P.J. Orchard, and D.A. Williams

ABSTRACT

BACKGROUND

Cerebral adrenoleukodystrophy is a severe form of X-linked adrenoleukodystrophy characterized by white-matter disease, loss of neurologic function, and early death. Elivaldogene autotemcel (eli-cel) gene therapy, which consists of autologous CD34+ cells transduced with Lenti-D lentiviral vector containing *ABCD1* complementary DNA, is being tested in persons with cerebral adrenoleukodystrophy.

METHODS

In a phase 2–3 study, we evaluated the efficacy and safety of eli-cel therapy in boys with early-stage cerebral adrenoleukodystrophy and evidence of active inflammation on magnetic resonance imaging (MRI). The primary efficacy end point was survival without any of six major functional disabilities at month 24. The secondary end points included overall survival at month 24 and the change from baseline to month 24 in the total neurologic function score.

RESULTS

A total of 32 patients received eli-cel; 29 patients (91%) completed the 24-month study and are being monitored in the long-term follow-up study. At month 24, none of these 29 patients had major functional disabilities; overall survival was 94%. At the most recent assessment (median follow-up, 6 years), the neurologic function score was stable as compared with the baseline score in 30 of 32 patients (94%); 26 patients (81%) had no major functional disabilities. Four patients had adverse events that were directly related to eli-cel. Myelodysplastic syndrome (MDS) with excess blasts developed in 1 patient at month 92; the patient underwent allogeneic hematopoietic stem-cell transplantation and did not have MDS at the most recent follow-up.

CONCLUSIONS

At a median follow-up of 6 years after lentiviral gene therapy, most patients with early cerebral adrenoleukodystrophy and MRI abnormalities had no major functional disabilities. However, insertional oncogenesis is an ongoing risk associated with the integration of viral vectors. (Funded by Bluebird Bio; ALD-102 and LTF-304 ClinicalTrials.gov numbers NCT01896102 and NCT02698579, respectively.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Williams can be contacted at dawilliams@childrens.harvard.edu or at Boston Children's Hospital, 300 Longwood Ave., Karp 08125.3, Boston, MA 02115.

Drs. Eichler and Duncan and Drs. Orchard and Williams contributed equally to this article.

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Adrenoleukodystrophy is an X-linked metabolic disease caused by pathogenic variants in *ABCD1* that lead to a deficiency in peroxisomal transporter ATP-binding cassette domain 1 (ABCD1 or adrenoleukodystrophy protein)[1,2] and the accumulation of saturated very-long-chain fatty acids. Cerebral adrenoleukodystrophy develops in approximately 35% of affected boys before adulthood.[1,3] Progressive white-matter inflammation and demyelination lead to the loss of cognitive and neurologic function, and early death ensues.[3,4] Magnetic resonance imaging (MRI) of the head with gadolinium enhancement is useful in diagnosing cerebral disease before the onset of clinical symptoms.[5,6]

Allogeneic hematopoietic stem-cell transplantation (HSCT) is the standard of care for cerebral adrenoleukodystrophy and can stabilize the disease and preserve function if it is performed at an early stage when demyelination is limited.[4,7,8] HLA-matched sibling donors are available for less than 20% of patients but historically have led to longer survival than that with HSCT from unrelated donors.[4,9-13] Allogeneic HSCT is limited by the lack of donors who are sufficiently HLA matched, the risk of graft failure, the risk of graft-versus-host disease (GVHD), and complications from chemotherapy and immunosuppression, all of which contribute to increased transplantation-related morbidity and mortality.[12]

Autologous hematopoietic stem-cell gene therapy may provide an alternative treatment without many of the risks associated with allogeneic HSCT. Clinical data from small numbers of patients with early-stage cerebral adrenoleukodystrophy[14-16] suggested that the use of lentiviral vectors containing *ABCD1* complementary DNA stabilized disease, but long-term follow-up in a larger patient population is lacking. We report the results of a completed initial 24-month study, a phase 2–3, multicenter, open-label study involving patients who received elivaldogene autotemcel (eli-cel) gene therapy transduced with Lenti-D lentiviral vector and who are participating in an ongoing long-term follow-up study.

Methods

Study Oversight

The study was sponsored by Bluebird Bio. Employees of Bluebird Bio developed the study protocol, available with the full text of this article at NEJM.org, with oversight and input from the coordinating investigator, disease experts, and an independent data and safety monitoring board. The protocol was approved by the requisite regulatory authorities and institutional ethics committees. The study was performed in accordance with the ethical principles outlined in the Declaration of Helsinki. The independent data and safety monitoring board reviewed the data. Employees of Bluebird Bio contributed to the study design; the collection, analysis, and interpretation of the data; and the writing of the manuscript. All the authors collected and had access to the study data and vouch for the completeness and accuracy of the data, the fidelity of the study to the protocol, and up-to-date reporting of adverse events. Additional details regarding the study design are provided in the protocol.

Trial Design and Eligibility

The 24-month study and the ongoing 13-year follow-up study were designed to assess the safety and efficacy of eli-cel gene therapy in boys 17 years of age or younger who had cerebral adrenoleukodystrophy at enrollment. We enrolled the patients at sites in Argentina, Australia, France, Germany, the United Kingdom, and the United States after obtaining written informed consent from their parents or guardians and assent from the patients, as appropriate, at the screening visit before initiation of any study procedures. Patients were eligible for the study if they had cerebral adrenoleukodystrophy confirmed by biochemical and genetic testing and if they had signs of early-stage cerebral disease with gadolinium enhancement on MRI of the brain that were characteristic of adrenoleukodystrophy,[17] a neurologic function score of 0 or 1 (range, 0 to 25, with higher scores indicating more severe deficits), and a Loes score of 0.5 to 9. The Loes score is a nonlinear, semiquantitative scale for the assessment of adrenoleukodystrophy white-matter lesions and atrophy on MRI; scores range from 0 to 34, with higher scores indicating more extensive disease, and a score of less than 0.5 considered to be normal. Both the Loes score and the neurologic function score have been validated for patients with adrenoleukodystrophy.[18,19] Patients were excluded from the study if they had a sibling who was HLA-matched and was willing and able to donate cells for HSCT.

CELL COLLECTION AND ELI-CEL INFUSION

CD34+ cells, obtained from patients by apheresis after mobilization with granulocyte colony-stimulating factor (G-CSF) with or without the hematopoietic stem-cell mobilizing agent plerixafor, were transduced with Lenti-D lentiviral vector under validated standard operating procedures, in accordance with Good Manufacturing Practice, to produce the patient-specific eli-cel drug product. The Lenti-D lentiviral vector we used in the current study is the same as the one we used in our original study in 2017.[14] Eli-cel was infused on day 0 after the patient underwent conditioning with busulfan (days −10 to −7) and cyclophosphamide (days −5 to −2), as described previously.[14] Additional information about eli-cel is provided in the Supplementary Appendix, available at NEJM.org.

CLINICAL, IMAGING, AND LABORATORY ASSESSMENTS

Patients were monitored for successful engraftment, which was defined by specific neutrophil and platelet counts (for the full definition, see the Supplementary Appendix), for disease progression, and for adverse events. Brain MRI scans were evaluated by an experienced neuroradiologist who was unaware of the patients' identities and clinical status. White-matter lesions were quantitated by means of the Loes score. The neurologic function score was used for the evaluation of the severity of gross neurologic dysfunction across multiple domains that assess for 15 disabilities (see the Supplementary Appendix for the definition of stabilization of the Loes and neurologic function scores). The six major functional disabilities evaluated were loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement.[10] Collection of adverse events for both the 24-month study and the long-term follow-up study is described in the Supplementary Appendix.

The primary efficacy end point was survival without any of the six major functional disabilities at month 24. The primary safety end point was acute (grade II or higher) or chronic GVHD by month 24. Secondary efficacy end points were the resolution of gadolinium enhancement on MRI at month 24, the time to sustained resolution of gadolinium enhancement on MRI (defined by a second MRI showing resolution of gadolinium enhancement and no subsequent evaluation indicating the presence of gadolinium enhancement), the change in the total neurologic function score from baseline to month 24, survival free of major functional disabilities over time, and overall survival. Exploratory efficacy end points were the change in the Loes score from baseline, the maintenance of a Loes score of 9 or lower or an increase of no more than 6 points from baseline; and the maintenance of a neurologic function score of 4 or lower without an increase of more than 3 points from baseline. The score on the Pediatric Quality of Life Inventory (PedsQL; normal range, 70 to 100 points, with higher scores indicating higher quality of life) was also an exploratory end point (for more details, see the Supplementary Appendix). Data from patients who withdrew from the study and whose final outcome was unknown were censored at the time they withdrew from the study.

Pharmacodynamic assessments included expression of adrenoleukodystrophy protein, evaluated by flow cytometric analysis, in peripheral-blood mononuclear cells and CD14+ cells, as described previously.[13] A quantitative polymerase-chain-reaction assay was used to determine the vector copy number in the drug product and in peripheral-blood samples.[14] Details of the analysis of vector integration sites are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The sample size for this study was not determined by formal statistical methods. The study was initially designed to treat up to 15 patients in order to have at least 12 evaluable patients. The study protocol was later amended to treat an overall cohort of approximately 30 patients; all efficacy analyses were performed on the overall cohort of 32 patients who received eli-cel. Additional details can be found in the Supplementary Appendix. For the analyses of the efficacy and safety end points, the widths of the confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. Statistical methods are primarily descriptive in nature and include point estimates and confidence limits as appropriate.

RESULTS

PATIENTS AND TREATMENT

From October 2013 through April 2019, a total of 32 patients 3 to 13 years of age (median, 6) received eli-cel; the median duration of follow-up

Table 1. Patient, Disease, and Transplantation Characteristics at Baseline.

Characteristic	Value (N=32)
Patients	
Median age (range) — yr	6 (3–13)
Median duration of follow-up (range) — mo	60.2 (13.4–106.9)
Median Loes score (range)*	2 (1–9)
Median neurologic function score (range)†	0 (0–1)
Median time from enrollment to eli-cel infusion (range) — days	67 (58–89)
Mobilization, apheresis, and conditioning	
Median dose of granulocyte colony-stimulating factor (range) — μg/kg/day	10.0 (8.9–12.5)
Median dose of plerixafor (range) — mg/kg/day‡	0.24 (0.24–0.24)
Median no. of aphereses per mobilization cycle (range)	2 (1–4)
Median no. of mobilization cycles per patient (range)	1 (1–1)
Median estimated average area under the curve of busulfan (range) — μmol×min/liter/day§	4717.5 (4039–5041)
Median total dose of cyclophosphamide (range) — mg/kg	199.2 (150.6–212.9)
Eli-cel drug product	
Median vector copy number (range) — copies/diploid genome	1.2 (0.5–2.7)
Median lentiviral vector positive cells (range) — %	45 (19–67)
Median eli-cel dose (range) — CD34+ cells/kg	11.4 (5.0–20.1)

* The Loes scale assesses adrenoleukodystrophy white-matter lesions and atrophy on MRI; scores range from 0 to 34, with higher scores indicating more extensive disease.
† The neurologic function scale ranges from 0 to 25, with higher scores indicating more severe deficits.
‡ Data are shown for the 11 patients who received plerixafor.
§ Because of an entry error, data are available for 31 patients.

as of February 1, 2023, was 60.2 months (interquartile range, 53.8 to 94.1; range, 13.4 to 106.9). At baseline, the neurologic function score ranged from 0 to 1, and the median Loes score was 2 (range, 1 to 9); no patients had any major functional disabilities. Apheresis of CD34+ cells (collected over a median of 2 days) was accomplished with a single mobilization cycle with the use of G-CSF, with the addition of plerixafor in 11 patients. Busulfan, at a dose that was adjusted for each patient, was administered to attain a target area under the curve of 17,000 to 21,000 μmol×min per liter. Baseline characteristics of the patients and details regarding mobilization, conditioning, and the drug product are shown in Table 1. On completion of 24 months of follow-up in the 24-month study, 29 patients enrolled in the long-term follow-up study; 3 patients did not enroll — 1 had died, and 2 had withdrawn from the study to undergo allogeneic HSCT. As of February 1, 2023, a total of 28 patients remained in the follow-up study; the median follow-up of these 28 patients was 72.4 months (interquartile range, 57.1 to 95.2; range, 39.8 to 106.9), including 21 patients (66%) who completed the visit at month 60; 1 patient was lost to follow-up at month 54.

END POINTS

After the eli-cel infusion, neutrophil engraftment was observed in all the patients by a median of 13 days (range, 11 to 41), and platelet engraftment in all the patients by a median of 32 days (range, 16 to 60). Figure 1 shows Kaplan–Meier curves for survival free of major functional disabilities and overall survival. A total of 29 of

32 patients (91%; 95% confidence interval [CI], 75 to 98) continued to be followed and had no major functional disabilities at month 24. Between infusion and month 24, a total of 3 patients (Patients 17, 15, and 19) did not meet the primary end point (see Fig. S1 in the Supplementary Appendix) and were included in the analysis as having had treatment failure. Patient 17 had major functional disabilities (total incontinence, loss of communication, cortical blindness, and wheelchair dependence beginning at month 9) and subsequently died during the study, as described previously.[14] Two patients were withdrawn from the study to undergo allogeneic HSCT because of disease progression: Patient 15 was withdrawn from the study by the investigator at month 13 to undergo allogeneic HSCT and subsequently died after withdrawal from the study, as described previously,[14] and imaging in Patient 19 showed disease progression that was deemed to be an indication for allogeneic HSCT.

During the follow-up period after month 24, cortical blindness developed in Patient 26 at approximately month 53. Patient 9 did not have any scheduled visits after month 36 and withdrew from the long-term follow-up study at month 54; therefore, the final outcome is unknown. Myelodysplastic syndrome (MDS) developed in Patient 3 at month 92 while the patient was in the follow-up study, and this patient underwent allogeneic HSCT (Fig. 1). As of February 1, 2023, a total of 26 of 32 patients (81%) have continued to be followed up and were free of major functional disabilities, with a median follow-up of 60.6 months (interquartile range, 56.3 to 92.6; range, 39.8 to 106.9).

At month 24, a total of 30 of 32 patients (94%) were alive (secondary end point of overall survival). No deaths occurred between month 24 and month 84 after eli-cel treatment. At month 48, overall survival was 94% and survival free of major functional disabilities was 91%. Clinical details for each patient are shown in Table S1.

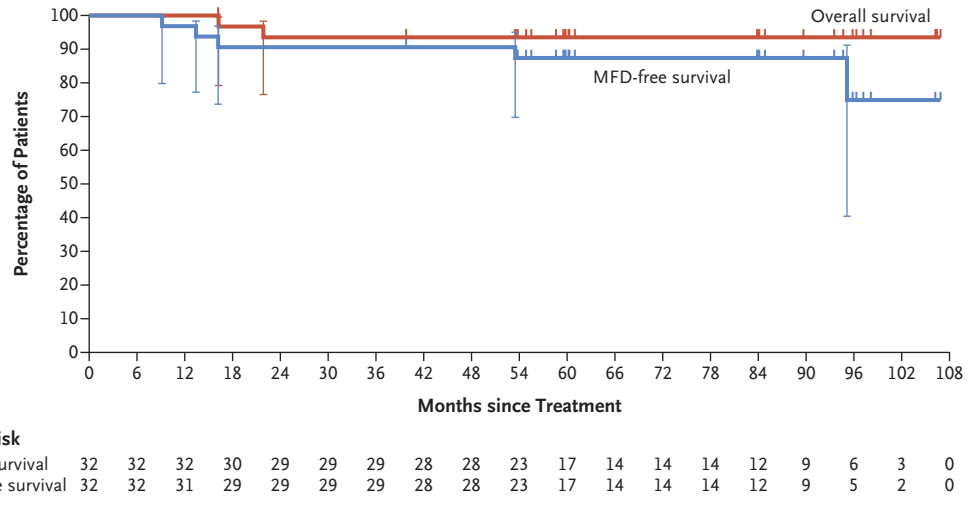

Figure 1. Kaplan–Meier Analyses of Overall Survival and Survival Free of Major Functional Disabilities.

Survival free of major functional disabilities (MFDs) was defined as survival without receipt of allogeneic hematopoietic stem-cell transplantation and free of the following six MFDs: loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement. Data from patients who withdrew from the study and whose final outcome was unknown were censored at the time they withdrew from the study. Twenty-six patients are MFD-free and remain in long-term follow-up. One patient died of transplantation-related causes after withdrawal from the study after undergoing allogeneic hematopoietic stem-cell transplantation, which had been performed owing to disease progression detected by radiography; this death is included in the Kaplan–Meier estimate. I bars indicate 95% confidence intervals; the widths of the confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing.

At month 24, the neurologic function score was stable in 29 of 30 evaluable patients (97%; 95% CI, 83 to 100); 28 of 30 evaluable patients (93%) had a neurologic function score of 0 or 1, one patient had a score of 2 to 3, and one patient had a score of more than 3. At the most recent assessment in either the 24-month study or the long-term follow-up study (median follow-up, 6 years), stability of the neurologic function score was seen in 30 of 32 patients (94%), and in most patients (28 of 32 patients; 88%) the neurologic function score remained at 0 or 1 (Fig. 2 and Fig. S3). Gadolinium enhancement that was present at baseline resolved by month 6 in 30 patients (94%) (Fig. 2); 26 of 30 evaluable patients (87%; 95% CI, 69 to 96) did not have gadolinium enhancement

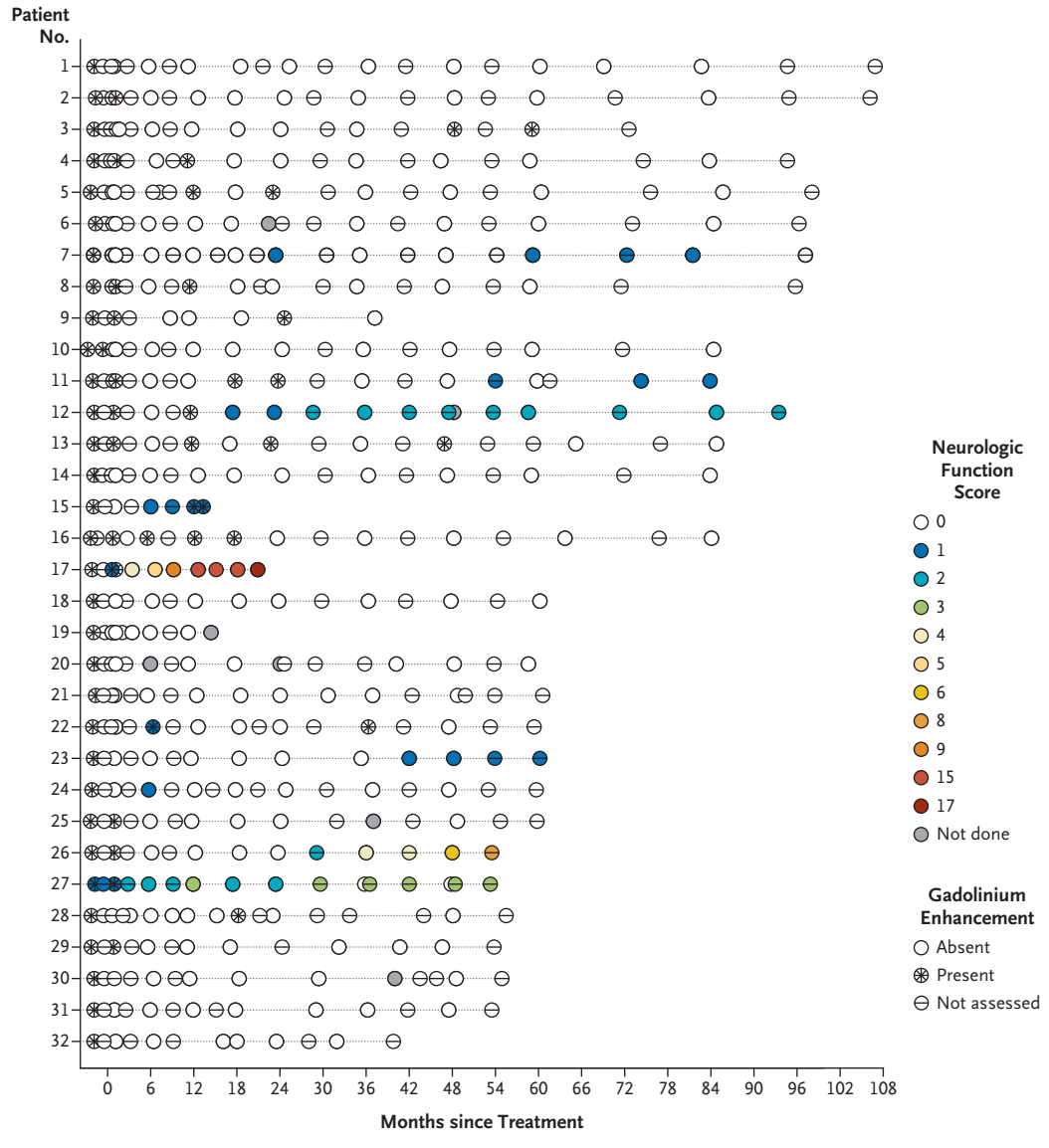

Figure 2. Individual Patient Results for Gadolinium Enhancement Status and Neurologic Function Score Over Time (Secondary End Points).

The neurologic function score ranges from 0 to 25, with higher scores indicating more severe deficits.

at month 24. A total of 30 of 32 patients (94%) received glucocorticoids to address underlying adrenal insufficiency between neutrophil engraftment and month 12 (Table S2). At month 24, Loes scores were stable in 24 of 30 evaluable patients (80%; 95% CI, 61 to 92). Figure 2 and Figures S2 and S3 show the neurologic function score and gadolinium-enhancement status (secondary end points) and changes in the Loes score (an exploratory end point) for each patient over time.

At the most recent follow-up in either the 24-month study or the long-term follow-up study, the median total PedsQL score (an exploratory end point) was 82.3 (range, 33.7 to 96.7). Scores were within the normal range in 23 of 32 patients (72%) (Figs. S4 and S5).

SAFETY

During the entire study period, including the follow-up period, 4 of 32 patients (12%) had adverse events related to eli-cel therapy. Serious adverse events were observed in 22 of 32 patients (69%). Serious infections occurred in 8 patients (25%). No GVHD was observed. Table S3 shows the incidence and timing of hospitalizations and visits to the intensive care unit, and Table S4 shows the incidence and timing of infection.

The incidence of adverse events was greatest in the period between conditioning and neutrophil engraftment, with all patients having adverse events and 8 of 32 patients (25%) having serious adverse events during this time; these events were generally associated with the conditioning regimen (Table 2 and Table S2). In the 24-month study, 3 patients had adverse events related to eli-cel therapy: hemorrhagic cystitis associated with BK virus (a serious event in 1 patient) and vomiting on the day of infusion that resolved the same day (in 2 patients). The median duration of hospitalization was 29 days (range, 15 to 54).

From month 24 through the most recent assessment in the long-term study, 10 of the 29 patients remaining in the study had at least one adverse event and 7 of these patients had at least one serious adverse event. A total of 5 patients had new onset of seizures; 4 of these 5 patients had evidence of a worse Loes score than they had had at baseline, defined as an increase in the score of at least 6 points; 3 of the 5 patients had a worse neurologic function score than they had had at baseline. As reported by Duncan et al. in this issue of the *Journal*,[20] MDS with excess blasts developed in 1 patient (Patient 3) at month 92 and was considered to be related to Lenti-D lentiviral vector; the patient subsequently underwent allogeneic HSCT at month 95 and had no indication of MDS recurrence at the most recent follow-up (month 120).

Integration-site analysis showed polyclonal reconstitution of peripheral blood in 18 of 32 patients (56%); the median of the highest number of unique integration sites across visits from infusion to month 24 in individual patients was 4821 (range, 582 to 14,500). Seven patients (22%) met the criteria for current persistent oligoclonality (see the Supplementary Appendix for the definition). In 1 patient (Patient 3), insertional oncogenesis associated with MDS was observed, with integration-site analysis revealing a predominant clone characterized by insertions in *PDRM16*, *MIR106A*, *CAMK2A*, *GAB3*, *TYK2*, and *SNX12* within the same clone.

PHARMACODYNAMIC ASSESSMENTS

The vector copy number in peripheral blood and CD14+ cells was stable after month 6 postinfusion (Fig. S6), and expression of transgene-derived protein in peripheral-blood leukocytes was observed in all patients (Fig. S7). Details of the relationship between the percentage of CD14+ cells expressing transgene-derived protein and the vector copy number in peripheral blood and between the percentage of CD14+ cells expressing transgene-derived protein and CD14+ vector copy number, as well as the relationship between the changes in Loes scores from baseline to month 24 and the vector copy number in peripheral blood at month 6 and between the changes in Loes scores from baseline to month 24 and transgene-derived protein expression in CD14+ cells, are shown in the Supplementary Results section of the Supplementary Appendix and Figures S8 and S9. Plasma levels of saturated very-long-chain fatty acids over time are shown in Figure S10.

DISCUSSION

This study of gene therapy with autologous genetically modified hematopoietic stem cells showed the possibility of lengthening disability-free survival in patients with cerebral adrenoleu-

Table 2. Incidence and Timing of Adverse Events.

Events	2-Yr Study (N=32)				13-Yr Follow-up Study (N=29)
	Mobilization to before Conditioning	Conditioning to before Neutrophil Engraftment	Neutrophil Engraftment through Month 12	After Month 12 through Month 24*	After Month 24 through Most Recent Assessment
	number of patients (percent)				
At least one adverse event	27 (84)	32 (100)	27 (84)	9 (28)	10 (34)
At least one adverse event attributed to mobilization or apheresis	15 (47)	0	0	0	0
At least one adverse event attributed to conditioning†	0	32 (100)	20 (62)	0	0
At least one adverse event attributed to eli-cel	0	2 (6)	1 (3)	0	1 (3)
Vomiting	0	2 (6)	0	0	0
Viral cystitis	0	0	1 (3)	0	0
Myelodysplastic syndrome	0	0	0	0	1 (3)
At least one serious adverse event‡	1 (3)	8 (25)	12 (38)	4 (12)	7 (24)
Blood and lymphatic system disorders	0	8 (25)	0	0	1 (3)
Cardiac disorders	0	0	0	1 (3)‡	0
Eye disorders	0	0	0	0	1 (3)
Gastrointestinal disorders	0	1 (3)	1 (3)	1 (3)	0
General disorders and administration site conditions	0	0	6 (19)	0	3 (10)
Hepatobiliary disorders	0	0	0	1 (3)	0
Infections and infestations	1 (3)	0	5 (16)	2 (6)	1 (3)
Injury, poisoning, and procedural complications	0	0	2 (6)	0	0
Metabolism and nutrition disorders	0	0	1 (3)	0	0
Musculoskeletal and connective-tissue disorders	0	0	0	1 (3)	0
Benign, malignant, or unspecified neoplasms	0	0	0	0	1 (3)
Nervous system disorders§	0	1 (3)	1 (3)	2 (6)	5 (17)
Psychiatric disorders	0	0	0	0	1 (3)
Renal and urinary disorders	0	0	0	1 (3)	0
Respiratory, thoracic, and mediastinal disorders	0	0	0	1 (3)	0

* Adverse events that were reported in a small number of patients who were assessed in the 24-month study after month 24 (given the timing of their most recent study visit) are also included.
† Individual events are listed in Table S2 in the Supplementary Appendix.
‡ Beginning at month 21, Patient 17 had 14 serious adverse events, including acute hepatic failure, viral infection, rhabdomyolysis, acute kidney injury, respiratory distress, and cardiorespiratory arrest leading to death; these events were considered to be related to disease progression.
§ Instances of seizures occurred in 5 patients.

kodystrophy. The current analyses extend interim results published in the *Journal*[14] to the full study population (32 patients), in which 26 of the 32 patients (Kaplan–Meier estimate, 75%) remain in the study and have been free of major functional disabilities for a median duration of 60.6 months, with a maximum duration of follow-up of 8.9 years in two patients. The incidence of serious adverse events related to eli-cel was low. During the long-term follow-up period, 5 patients had new onset of seizures, and 4 of these 5 patients had evidence of worsening Loes scores. At month 48, overall survival was 94% and survival free of major functional disabilities was 91%. The rates that have been published with respect to allogeneic HSCT in patients with similar clinical status at baseline are 77.8% for 4-year overall survival and 63.2% for the percentage of patients with no major functional disabilities.[12] However, comparative inferences cannot be drawn since these populations were not directly compared.[12]

As expected with autologous therapy, GVHD did not occur, and although conditioning-related serious infections occurred, they did not result in death. These findings contrast with what has been shown to occur with allogeneic HSCT during the peritransplantation period in which serious infections (in up to 29% of patients),[10] acute GVHD in the first 100 days (in 18 to 31% of patients),[9,10,12] and graft failure (in up to 24% of patients with grafts from unrelated donors) can contribute to transplantation-related mortality, which remains high at 8 to 15% in persons with cerebral adrenoleukodystrophy.[10,12,13] The duration of hospitalization for patients undergoing transplantation was shorter with eli-cel (median, 29 days [range, 15 to 54]) than with allogeneic HSCT (51 days [range, 25 to 240] as reported in 59 patients in a contemporaneous study).[12]

Preclinical in-vitro assays for insertional mutagenesis with the Lenti-D lentiviral vector, which contains one promoter–enhancer sequence in a self-inactivating configuration, did not reveal any indication of insertional oncogenesis. However, nonfatal MDS with excess blasts developed in one patient in the 24-month study. A predominant hematopoietic clone, characterized by an insertion site in *PRDM16* with multiple other insertions in the same clone, was identified at the time of the MDS diagnosis; the case was considered to be probably mediated by Lenti-D lentiviral vector insertion. The completed companion study involving patients with cerebral adrenoleukodystrophy, ALD-104 (ClinicalTrials.gov number, NCT03852498),[21] investigated eli-cel therapy but with a different conditioning regimen. As reported by Duncan et al., in ALD-104, six cases of hematologic cancer have been recorded in either the 24-month or the long-term follow-up study (five cases of MDS and one case of acute myeloid leukemia).[20]

It is hypothesized that the effector cell needed to express functional protein and preserve neurologic function with both allogeneic HSCT and gene therapy is the microglial cell or a similar cell derived from a monocyte–macrophage myeloid lineage.[22-26] Here, we showed that the vector copy number and expression of transgene-derived protein in peripheral-blood myeloid cells remained stable over time. There did not appear to be a correlation between the vector copy number in the eli-cel and changes in the Loes score in the larger population with long-term follow-up described in the current study.[16]

A limitation of the current study is the small number of patients included who had a high baseline Loes score. Additional longer-term follow-up, including data on neuropsychiatric testing outcomes, is needed to fully characterize the long-term efficacy and safety of eli-cel.

Most patients with cerebral adrenoleukodystrophy in this study appear to have benefited from eli-cel, with benefit shown over a median duration of follow-up of 60.2 months, and up to 8.9 years in two patients, and with a low incidence of serious adverse events. Clonal expansion that can evolve into MDS should be considered in the context of the known morbidity and mortality associated with allogeneic HSCT. Longer-term follow-up is needed to determine whether the efficacy observed to date, in terms of survival free of major functional disabilities and overall survival, will be maintained over the longer term. However, these data suggest that eli-cel may be a treatment option for selected patients with cerebral adrenoleukodystrophy who lack a suitable stem-cell donor.

The views expressed are those of the authors and do not necessarily represent the views of the National Health Service, the National Institute for Health and Care Research, or the Department of Health.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

The authors' full names and academic degrees are as follows: Florian Eichler, M.D., Christine N. Duncan, M.D., Patricia L. Musolino, M.D., Ph.D., Troy C. Lund, M.D., Ashish O. Gupta, M.D., Satiro De Oliveira, M.D., Adrian J. Thrasher, M.D., Patrick Aubourg, M.D., Jörn-Sven Kühl, M.D., Daniel J. Loes, M.D., Hernan Amartino, M.D., Nicholas Smith, M.D., Juliana Folloni Fernandes, M.D., Caroline Sevin, M.D., Ph.D., Raman Sankar, M.D., Ph.D., Shaun A. Hussain, M.D., Paul Gissen, M.D., Jean-Hugues Dalle, M.D., Ph.D., Uwe Platzbecker, M.D., Gerald F. Downey, M.Sc., Elizabeth McNeil, M.D., Laura Demopoulos, M.D., Andrew C. Dietz, M.D., Himal L. Thakar, M.D., Paul J. Orchard, M.D., and David A. Williams, M.D.

The authors' affiliations are as follows: Massachusetts General Hospital and Harvard Medical School (F.E., P.L.M.) and Dana–Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School (C.N.D., D.A.W.), Boston, Bluebird Bio, Somerville (G.F.D., L.D., A.C.D., H.L.T.), and McNeil Pediatrics Consultancy, Sudbury (E.M.) — all in Massachusetts; the Division of Blood and Marrow Transplantation, Department of Pediatrics, University of Minnesota (T.C.L., A.O.G., P.J.O.), and Midwest Radiology (D.J.L.) — both in Minneapolis; David Geffen School of Medicine, University of California, Los Angeles, Los Angeles (S.D.O., R.S., S.A.H.); University College London Great Ormond Street Hospital Institute of Child Health and Great Ormond Street Hospital NHS Trust, London (A.J.T., P.G.); INSERM, Université Paris–Saclay, Hôpital Kremlin-Bicêtre (P.A.), the Reference Center for Leukodystrophies, Hôpital Kremlin-Bicêtre, Assistance Publique–Hôpitaux de Paris, Université Paris–Saclay (C.S.), and Robert-Debre Hospital, GHU Nord-Université de Paris (J.-H.D.) — all in Paris; the Departments of Pediatric Oncology/Hematology/Hemostaseology (J.-S.K.) and Hematology, Cellular Therapy, Hemostaseology and Infectious Diseases (U.P.), University Hospital Leipzig, Leipzig, Germany; Instituto Neurogenia and Hospital Universitario Austral — both in Buenos Aires (H.A.); Women's and Children's Health Network and the University of Adelaide — both in Adelaide, SA, Australia (N.S.); ITACI/Instituto da Criança-Hospital das Clínicas da Universidade de São Paulo, Sao Paulo (J.F.F.); and Shape Therapeutics, Seattle (A.C.D.).

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