GlobalData.

Clinical Trial Information			
Trial Title	Effect of Lentiviral (Lv) Hematopoietic Stem Cell Gene Therapy in Subjects with Early- onset Metachromatic Leukodystrophy (MLD)		
Drug(s)/Molecule(s)	atidarsagene autotemcel;	**Trial Identifier**	GDCT0369560
Secondary ID(s)	GDC20026131		
Sponsor (s)	Orchard Therapeutics Plc	**Indication**	Metachromatic Leukodystrophy (MLD)
Trial Status	Completed	**Trial Phase**	Phase III

Clinical Trial Details	
Trial Title	Effect of Lentiviral (Lv) Hematopoietic Stem Cell Gene Therapy in Subjects with Early- onset Metachromatic Leukodystrophy (MLD)
Official Title	Effect of Lentiviral (Lv) Hematopoietic Stem Cell Gene Therapy in Subjects with Early- onset Metachromatic Leukodystrophy (MLD)
Study Type	Expanded Access
Therapy Type	Monotherapy
Estimated End Date	01 Mar 2019
Study Designs	
Purpose	The purpose of this study was to assess effects of lentiviral (LV) hematopoietic stem cell gene therapy (HSC-GT) in subjects with early-onset metachromatic leukodystrophy subjects with ≤8 yrs post-treatment follow-up (FU).
Primary Outcome Measure(s)/Objective(s)	To assess the efficacy included motor and cognitive function, MR measure-ments of demyelination and atrophy, and electroneurographic recordings to measure nerve conduction velocity (NCV).
Trial Description	This was an expanded access study to assess effects of lentiviral (LV) hematopoietic stem cell gene therapy (HSC-GT) in subjects with early-onset metachromatic leukodystrophy subjects with ≤8 yrs post-treatment follow-up (FU). Subjects received lentiviral (LV) hematopoietic stem cell gene therapy (HSC-GT). A total of nine subjects were enrolled in the study.

Sponsor(s)/Collaborator(s)
Sponsor(s) - Type & Details

Sponsor	Orchard Therapeutics Plc

Drug Details

Primary Interventions(s)	**Generic Name** / **Route of Administration** atidarsagene autotemcel / Intravenous
Drug Name	atidarsagene autotemcel (Marketed Drug)
Drug Description	Atidarsagene autotemcel (libmeldy) is a gene therapy containing an autologous CD34+ cell enriched population that contains hematopoietic stem and progenitor cells transduced ex vivo using a lentiviral vector encoding the human arylsulfatase A gene. It is formulated as dispersion concentrate solution for intravenous route of administration. Libmeldy is indicated treatment of metachromatic leukodystrophy (MLD) characterized by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity in children with late infantile or early juvenile forms, without clinical manifestations of the disease, in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline. OTL-200 (GSK-2696274) is under development for the treatment of metachromatic leukodystrophy. It is an ex-vivo stem cell gene therapy administered intravenously as an infusion. It consists of autologous CD34+ cells transfected with lentiviral vector containing the human arylsulfatase A cDNA.
Mechanism of Action	OTL-200 (GSK-2696274) exerts neuroregenerative effects. Autologous CD34+ cells transfected with lentiviral vector containing the human arylsulfatase A cDNA includes taking cells called CD34+ cells from the blood of the affected patient and introducing the gene for the lacking enzyme into these cells, outside of the body. To introduce the gene into the cells, a man-made virus (lentiviral vector) is used. The cells are then infused back into the patient, where they are expected to produce and replace the lacking enzyme arylsulfatase A. The replacement of the lacking enzyme reduces the accumulated sulfatides and alleviates the condition.
ATC Classification	N07XX Other nervous system drugs
Target	Arylsulfatase A (Cerebroside Sulfatase or ASA or ARSA or EC 3.1.6.8)

Patient Details

Age	
Healthy Subject(s)	No
Subject(s) Type	Early Onset Disease, Pediatric

Participant Criteria (Inclusion)	Subjects with early- onset metachromatic leukodystrophy (MLD).

Trial Results	
No. of Subjects Enrolled	9
No. of Subjects Analyzed	9
Endpoint Classification	Efficacy, Safety
End Point Status	Achieved
Efficacy Results	**April 14, 2024** Presented at the 50th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT 2024), April 14 - 17, 2024, Glasgow, Scotland, United Kingdom Atidarsagene Autotemcel (Haematopoietic Stem Cell Gene Therapy) Preserves Cognitive and Motor Development in Metachromatic Leukodystrophy with up to 12 Years Follow-up Session: GS2 Presidential Symposium Abstract No.: GS02-05 Valeria Calbi et al.Based on the pooled results of GDC30014383, NCT01560182 and GDC20026131 presented, GlobalData inferred that stable engraftment of gene-corrected cells and restoration of atidarsagene autotemcel activity in peripheral blood mononuclear cells to normal or supranormal levels and in cerebrospinal fluid to normal levels were demonstrated by all subjects , which were sustained throughout follow-up.https://ebmt2024.abstractserver.com/program/#/details/presentations/809 **March 14, 2024** Presented at the 2024 American College of Medical Genetics and Genomics (ACMG 2024) Annual Clinical Genetics Meeting, March 12 - 16, 2024, Toronto, Canada Atidarsagene Autotemcel (Hematopoietic Stem Cell–Gene Therapy) Preserves Cognitive and Motor Development in Metachromatic Leukodystrophy With up to 12 Years Follow-Up Session: Platform Presentations Abstract No.: P005 Francesca Fumagalli et al.Based on the pooled results of GDC30014383, NCT01560182 and GDC20026131 presented, GlobalData inferred that all subjects demonstrated stable engraftment of gene-corrected cells and restoration of arylsulfatase A activity in peripheral blood to normal or supranormal levels by 3 months post-treatment and restoration in cerebrospinal fluid to normal levels by 3-6 months post-treatment, which were sustained throughout follow-up. The risk of experiencing severe motor impairment or death was significantly reduced in the pre-symptomatic late-infantile (PSLI, $p<0.001$),

	pre-symptomatic early-juvenile (PSEJ, p=0.042), and early-symptomatic early-juvenile (ESEJ, able to walk independently and without cognitive impairment prior to treatment, p<0.001) treated subgroups versus MLD subtype-matched natural history subjects. Atidarsagene autotemcel treatment resulted in substantial improvements in motor and cognitive outcomes as compared with natural history particularly among subjects treated before symptom onset. Over 95% of treated PSLI and PSEJ subjects retained the ability to walk at last follow-up, and the majority of treated PSLI, PSEJ, and ESEJ patients experienced clinically meaningful preservation of cognitive abilities. Furthermore, post hoc analyses on loss of speech, identified by caregivers as having a high impact on patient and caregiver QoL, revealed that arsa-cel reduced the risk of experiencing loss of speech in the PSLI (p<0.001), PSEJ (p=0.042), and ESEJ (p=0.032) treated subgroups as compared to MLD subtype-matched natural history subjects, most of whom lost all speech. https://acmg.planion.com/Web.User/AbstractDet?ACCOUNT=ACMG&ABSID=353333&CONF=AM24&ssoOverride=OFF&CKEY=79L8B2L00 **September 2019** Presented at the 13th European Paediatric Neurology Society Congress (EPNS 2019), September 17 - 21, 2019, Athens, Greece Long term effect of Lentiviral (LV) Hematopoietic Stem Cell Gene Therapy (HSC-GT) on the nervous system in early-onset Metachromatic Leukodystrophy (MLD) Session: PARALLEL SESSION 2D: Neurometabolic Disorders I Abstract no: OC038 Fenella Kirkham et al. Based on the results presented, GlobalData inferred that nine subjects were analyzed in the study. After gene therapy, subjects showed normal psychomotor development or slower progression of motor and cognitive symptoms and initial slight worsening of brain MR scores and NCV was followed by stabilization. While motor function deteriorated in subjects treated after symptom onset, brain MR and IQ score stabilized in most during follow-up. Prevented stabilized or delay motor and cognitive decline and progressive demyelination and atrophy with a greater effect in subjects treated prior to symptom onset. http://www.epns2019.org/assets/EPNS_2019_ABSTRACT_BOOK_high_v3.pdf (Page 28) Based on the results reported, hematopoietic stem cell gene therapy had no overt manifestations in subjects with early-onset metachromatic leukodystrophy subjects with ≤8 yrs post-treatment follow-up (FU). Based on the results reported, no overt manifestations were observed with hematopoietic stem cell gene therapy in subjects with early-onset metachromatic leukodystrophy subjects with ≤8 yrs post-treatment follow-up (FU).
Safety Result	**April 14, 2024** Presented at the 50th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT 2024), April 14 - 17, 2024, Glasgow, Scotland, United Kingdom Atidarsagene Autotemcel (Haematopoietic Stem Cell Gene

	Therapy) Preserves Cognitive and Motor Development in Metachromatic Leukodystrophy with up to 12 Years Follow-up Session: GS2 Presidential Symposium Abstract No.: GS02-05 Valeria Calbi et al.Based on the pooled results of GDC30014383, NCT01560182 and GDC20026131 presented, GlobalData inferred that three treated subjects died all considered unrelated to atidarsagene autotemcel. https://ebmt2024.abstractserver.com/program/#/details/presentations/809 **March 14, 2024** Presented at the 2024 American College of Medical Genetics and Genomics (ACMG 2024) Annual Clinical Genetics Meeting, March 12 - 16, 2024, Toronto, Canada Atidarsagene Autotemcel (Hematopoietic Stem Cell–Gene Therapy) Preserves Cognitive and Motor Development in Metachromatic Leukodystrophy With up to 12 Years Follow-Up Session: Platform Presentations Abstract No.: P005 Francesca Fumagalli et al.Based on the pooled results of GDC30014383, NCT01560182 and GDC20026131 presented, GlobalData inferred that most natural history subjects experienced rapid motor and cognitive decline, progressing to a severely debilitated state or death. Three treated subjects died, all considered unrelated to atidarsagene autotemcel. There were no serious adverse events related to atidarsagene autotemcel no malignancies, and no evidence of abnormal clonal expansion or replication-competent lentivirus. The only atidarsagene autotemcel-related AEs were 6 events of transient and low titer anti-ARSA antibodies with no impact on pharmacodynamic or clinical outcomes.https://acmg.planion.com/Web.User/AbstractDet?ACCOUNT=ACMG&ABSID=353333&CONF=AM24&ssoOverride=OFF&CKEY=79L8B2L00 **September 2019** Presented at the 13th European Paediatric Neurology Society Congress (EPNS 2019), September 17 - 21, 2019, Athens, Greece Long term effect of Lentiviral (LV) Hematopoietic Stem Cell Gene Therapy (HSC-GT) on the nervous system in early-onset Metachromatic Leukodystrophy (MLD) Session: PARALLEL SESSION 2D: Neurometabolic Disorders I Abstract no: OC038 Fenella Kirkham et al. Based on the results presented, GlobalData inferred that hematopoietic stem cell gene therapy was safe and well-tolerated treatment option with a positive benefit-risk profile. http://www.epns2019.org/assets/EPNS_2019_ABSTRACT_BOOK_high_v3.pdf (Page 28)
Pharmacokinetic Evaluation	
Statistical Method (if any)	
Conclusion	The trial was completed. Based on the results reported, GlobalData concluded

	that no overt manifestations are observed with hematopoietic stem cell gene therapy in subjects with early-onset metachromatic leukodystrophy subjects with ≤8 yrs post-treatment follow-up (FU).

Trial Cost Overview

Trial Cost By Year

Trial Cost By Components

Investigators Information			
Name	Fabio Ciceri	Role	Co-Author
Specialty	Oncology; Hematology	Board Certification	
Primary Designation	Professor	Associated Organization	Vita-Salute San Raffaele University
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State	Lombardy	Country	Italy

Similar studies done by Investigator

Investigators Information			
Name	Maurizio F Ormezzano	Role	
Specialty	Cardiology; Interventional Cardiology	Board Certification	
Primary Designation	Professor	Associated Organization	IRCCS Policlinico San Matteo
Contact Number	39-382-501598	Email	m.ferrario@smatteo.pv.it
State	Pavia	Country	Italy

Investigators Information			
Name	Giancarlo Comi	Role	Co-Author
Specialty	Neurology; Molecular Medicine	Board Certification	

Primary Designation	Professor	Associated Organization	Vita-Salute San Raffaele University
Contact Number	39-2-26434771	Email	comi.giancarlo@hsr.it; g.comi@hsr.it
State	Milan	Country	Italy

Investigators Information			
Name	Alessandro Aiuti	Role	Co-Author
Specialty	Molecular genetics; Hematology; Pediatric Medicine	Board Certification	
Primary Designation	Professor	Associated Organization	Vita-Salute San Raffaele University
Contact Number	39-2-26434671; 39-2-6434668	Email	alessandro.aiuti@hsr.it; a.aiuti@hsr.it
State	Milan	Country	Italy

Similar studies done by Investigator

Investigators Information			
Name	Paola M V Rancoita	Role	Co-Author
Specialty	Nursing; Biostatistics	Board Certification	
Primary Designation	Professor	Associated Organization	Vita-Salute San Raffaele University
Contact Number	39-2-26433844; 39-2-91751554	Email	rancoita.paolamaria@unisr.it
State	Milan	Country	Italy

Similar studies done by Investigator

Location(s) (1)

Region	Country	State	Trial Site	Address	Status
Europe	Italy				Completed

Investigator Affiliated Site(s)(17)					
Region	**Country**	**State**	**Trial Site**	**Address**	**Status**
North America	United States	Massachusetts	Boston Children's Hospital	300 Longwood Avenue, Boston, MA 02115	
North America	United States	Connecticut	VA Connecticut Healthcare System	950 Campbell Avenue, West Haven, CT 06516	
Europe	Italy	Lombardy	Pope John XXIII Hospital	Piazza OMS, 1, 24127 Bergamo BG, Italia	
Europe	Italy	Lombardy	Fondazione Centro San Raffaele del Monte Tabor	Olgettina 60, 20132 Milano, Italia	
Europe	Italy	Lombardy	IRCCS Policlinico San Matteo Foundation	Viale Camillo Golgi, 19, 27100 Pavia PV, Italy	
Europe	Italy	Veneto	Azienda Ospedaliera di Padova	Via Giustiniani, 2 - 35128 Padova	
Europe	Italy	Lombardy	Institute of Experimental Neurology	Milan, Lombardy, 20132, Italy	
Europe	Italy	Lombardy	Istituti Ospitalieri di Cremona	Viale Concordia n 1, 26100 Cremona	
Europe	Italy	Lazio	Bambino Gesu Children’s Hospital	Piazza Sant'Onofrio, 4 - 00165 Roma	
Europe	Italy	Lombardy	IRCCS San Raffaele Hospital	via Olgettina 60, 20132 Milano	
Europe	Italy	Lombardy	San Raffaele Scientific Institute	Via Olgettina n. 60, Milano, 20132	

Europe	Italy	Veneto	University of Padova	Via Giustiniani, 2 - 35128 Padova	
Europe	Italy	Umbria	University of Perugia	piazza Università, 1 06123 Perugia	
Europe	Italy	Lombardy	Vita-Salute San Raffaele University	Via Olgettina, 58 – 20132 MILANO	
Europe	Italy	Lombardy	Centro Scienze della Natalita dell'Ospedale San Raffaele	via Olgettina 60, 20132 Milano, Italia	
Europe	Italy	Lombardy	San Raffaele Telethon Institute for Gene Therapy	Via Olgettina Milano, 60, 20132 Milano MI, Italy	
North America	United States	Massachusetts	Dana-Farber/Boston Children's Cancer and Blood Disorders Center	300 Longwood Avenue Boston, MA 02115	

Contact Detail(s)

Contact Person Name	Phone Number	Email ID	Address	State	Country	Region
Alessandro Aiuti	39-2-26431; 39-2-26433838; 39-2-26434671; 39-2-6434668	a.aiuti@hsr.it alessandro.aiuti@hsr.it	Vita-Salute San Raffaele University, Ospedale San Raffaele, Milano, via Olgettina 60, 20132 Milano, Italy	Milan	Italy	Europe

Site Coordinator Detail(s)

Site Coordinator Name	Email	Phone	Address	Organization	Site Name
Alessandro Aiuti	a.aiuti@hsr.it	39-2-26431; 39-	Vita-Salute San Raffaele	Vita-Salute San Raffaele	Vita-Salute San Raffaele

	alessandro.aiuti@hsr.it	2-26433838; 39-2-26434671; 39-2-6434668	University, Ospedale San Raffaele, Milano, via Olgettina 60, 20132 Milano, Italy	University	University, Milan, 20132

Key Trial Events (7)

Event Date	Event Brief	Event Type	Source
14 Apr 2024	Atidarsagene Autotemcel (Haematopoietic Stem Cell Gene Therapy) Preserves Cognitive and Motor Development in Metachromatic Leukodystrophy with up to 12 Years Follow-up Trial pooled results updated	Pooled Results	https://ebmt2024.abstractserver.com/program/#/details/presentations/809
18 Mar 2024	FDA Approves First Gene Therapy for Children with Metachromatic Leukodystrophy	Trial Update	https://www.prnewswire.com/news-releases/fda-approves-first-gene-therapy-for-children-with-metachromatic-leukodystrophy-302091811.html
14 Mar 2024	Atidarsagene Autotemcel (Hematopoietic Stem Cell–Gene Therapy) Preserves Cognitive and Motor Development in Metachromatic Leukodystrophy With up to 12 Years Follow-Up Trial pooled results updated	Pooled Results	https://acmg.planion.com/Web.User/AbstractDet?ACCOUNT=ACMG&ABSID=353333&CONF=AM24&ssoOverride=OFF&CKEY=79L8B2L00
18 Sep 2023	Orchard Therapeutics Announces Acceptance of Biologics License Application for OTL-200 in MLD and Receives Priority Review	Trial Update	https://www.globenewswire.com/news-release/2023/09/18/2744644/0/en/Orchard-Therapeutics-Announces-Acceptance-of-Biologics-License-Application-for-OTL-200-in-MLD-and-Receives-Priority-Review.html
09 Feb 2021	Orchard Therapeutics announces interim data for OTL-203 showing positive clinical results in multiple disease manifestations of mucopolysaccharidosis type I Hurler	Trial Update	https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-announces-interim-data-otl-203-showing

	syndrome (MPS-IH)		
19 Nov 2020	Orchard Therapeutics announces FDA clearance of IND application for OTL-200 for Metachromatic Leukodystrophy (MLD)	Trial Update	https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-announces-fda-clearance-ind-application-otl
16 Oct 2020	Orchard Therapeutics receives positive CHMP opinion for Libmeldy for the treatment of early-onset Metachromatic Leukodystrophy (MLD)	Trial Update	https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-receives-positive-chmp-opinion-libmeldytm

History of changes

Modified Date	Update Type	Description	From Data	To Data	Source Date	Source Type	Source
19-Apr-2024	Trial Result	Pooled Results Updated			14-Apr-2024	Conferences	https://ebmt2024.abstractserver.com/program/#/details/presentations/809
19-Mar-2024	Trial Result	Pooled Results Updated			14-Mar-2024	Conferences	https://acmg.planion.com/Web.User/AbstractDet?ACCOUNT=ACMG&ABSID=353333&CONF=AM24&ssoOverride=OFF&CKEY=79L8B2L00
19-Sep-2023	Subjects	Trial Subjects Updated	Early Onset Disease	Early Onset Disease, Pediatric	18-Sep-2023	Company Press Release	https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-announces-acceptance-biologics-license

Sources

- Francesca Fumagalli, "Long term effect of Lentiviral (LV) Hematopoietic Stem Cell Gene Therapy (HSC-GT) on the nervous system in early-onset Metachromatic Leukodystrophy (MLD)", The 13th Annual Meeting of the European Paediatric Neurology Society Congress (EPNS 2019), Session: PARALLEL SESSION 2D: Neurometabolic Disorders I, Abstract No.: OC038, 17-21 Sep 2019

- Francesca Fumagalli, "Atidarsagene Autotemcel (Hematopoietic Stem Cell–Gene Therapy)

Preserves Cognitive and Motor Development in Metachromatic Leukodystrophy With up to 12 Years Follow-Up",The 2024 American College of Medical Genetics and Genomics (ACMG 2024) Annual Clinical Genetics Meeting, Session: Platform Presentations, Abstract No.: P005, 12-16 Mar 2024

- Valeria Calbi, "Atidarsagene Autotemcel (Haematopoietic Stem Cell Gene Therapy) Preserves Cognitive and Motor Development in Metachromatic Leukodystrophy with up to 12 Years Follow-up", The 50th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT 2024), Session: GS2 Presidential Symposium, Abstract No.: GS02-05, 14-17 Apr 2024

- Orchard Therapeutics, "Orchard Therapeutics Announces FDA Clearance of IND Application for OTL-200 for Metachromatic Leukodystrophy (MLD)", 19 Nov 2020

- Orchard Therapeutics, "Orchard Therapeutics Receives Positive CHMP Opinion for Libmeldy for the Treatment of Early-Onset Metachromatic Leukodystrophy (MLD)", 16 Oct 2020
- Orchard Therapeutics Plc., "Orchard Therapeutics Announces Interim Data for OTL-203 Showing Positive Clinical Results in Multiple Disease Manifestations of Mucopolysaccharidosis Type I Hurler Syndrome (MPS-IH)", 09 Feb 2021
- Orchard Therapeutics Plc., "Orchard Therapeutics Announces Acceptance of Biologics License Application for OTL-200 in MLD and Receives Priority Review", 18 Sep 2023 (Subject's)

PR Newswire, News and Information Distribution Service Providers, "FDA Approves First Gene Therapy for Children with Metachromatic Leukodystrophy", 18 Mar 2024

Last Reviewed on 19 Apr 2024