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MADE FOR MORE

RESULTS OF PIVOTAL TRIALS IN PEDIATRIC PATIENTS

TRECONDI®
TREOSULFAN

IMPROVING PERSPECTIVES

PEDIATRIC PATIENTS WITH MALIGNANT DISEASES

PIVOTAL PHASE II TRIAL: MALIGNANT DISEASES[1]

Kalwak K, Mielcarek M, Patrick K, Styczynski J, Bader P, Corbacioglu S, Burkhardt B, Sykora KW, Drabko K, Gozdzik J, Fagioli F, Greil J, Gruhn B, Beier R, Locatelli F, Müller I, Schlegel PG, Sedlacek P, Stachel KD, Hemmelmann C, Möller AK, Baumgart J, Vora A

BACKGROUND

Children needing allogeneic stem cell transplantation (alloHSCT) for various hematologic malignancies usually receive a conditioning treatment based on either Bu or TBI, which, however, are associated with a considerable risk of toxicities. In the past use of Treosulfan for conditioning treatment in children with various disorders was reported, showing its potential use in this field.

MEDIAN FOLLOW-UP (RANGE)

41.8 mo (24.2 - 57.5)

STUDY AIM

Safety and efficacy of BSA-adapted Treo-based conditioning in pediatric patients with hematologic malignancies; contribute to a PK model.

STUDY DESIGN

DAYS	-7	-6	-5	-4	-3	-2	-1	0
TREOSULFAN i.v. (BSA adapted: 10, 12 or 14g/m²/day over 120min, prior to Fludarabine)		x	x	x				
Fludarabine i.v. (30 mg/m²/day)	x	x	x	x	x			
Thiotepa i.v (2 x 5mg/kg/day)						xx		
Allogeneic stem cell transplantation								x

CHILDREN WITH MALIGNANT HEMATOLOGIC DISEASE

Total	n=65
ALL	n=23
AML	n=29
MDS	n=10
JMML	n=3

SEX

Female	n=23	(35.4%)
Male	n=42	(64.6%)

AGE OF PATIENTS

28 days to 17 years
(median age 11 years)

DISEASE STATE: NUMBER OF COMPLETE REMISSION

CR1	n=41	(63.1%)
CR2	n=10	(15.4%)
CR≥3	n=1	(1.5%)

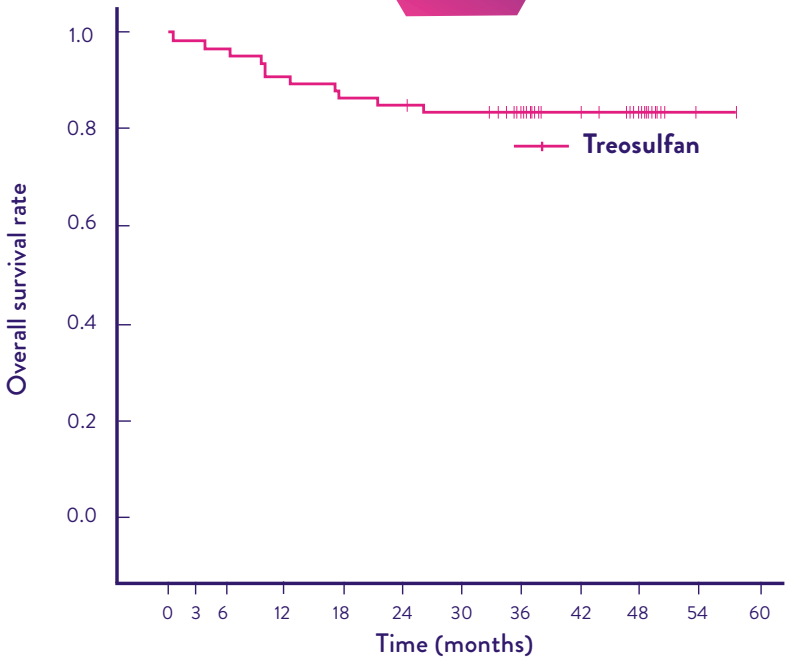
DONOR TYPE [N (%)]

Matched sibling	n=11	(16.9%)
Matched family	n=1	(1.5%)
Matched unrelated	n=53	(81.5%)

SOURCE [N (%)]

Bone marrow	n=33	(50.8%)
Peripheral blood	n=32	(49.2%)

TRIAL OUTCOMES



	Treosulfan
Number of subjects at risk	65
Events	11 (16.9%)
Censored	54 (83.1%)
Rate at 36 months[a] [%]	83.0
90% CI	(73.7, 89.3)

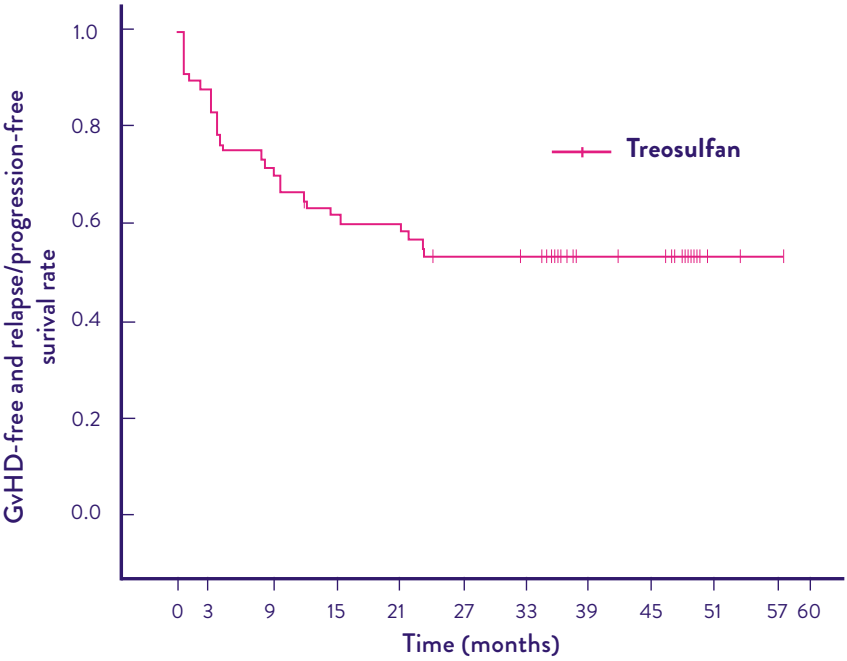
[a]Based on Kaplan-Meier estimates

- Complete donor chimerism 98.4% (on day +28)
- 3y Overall survival (OS) 83%: ALL-pts. 78.3%, AML-pts. 86.2%, MDS-pts. 90%
- 3y Relapse/Progression-free survival (RFS/PFS) 73.6%
- 3y GvHD-free and relapse/progression-free survival (GRFS) 56.7%

	N	n	Rate at 36 months [%] (90% CI)
Overall	65	17	73.6 (63.3, 81.5)
Disease			
ALL	23	7	69.6 (50.8, 82.3)
AML	29	6	79.3 (63.5, 88.8)
MDS	10	1	88.9 (54.3, 97.8)
JMML	3	3	0.0 (NA,NA*)
Treosulfan dose			
10 g/m^2/day	5	1	80.0 (31.4, 95.8)
12 g/m^2/day	23	6	73.9 (55.3, 85.7)
14 g/m^2/day	37	10	72.5 (58.2, 82.7)
Number of HSCT			
1st	60	14	76.4 (65.9, 84.1)
2nd	5	3	40.0 (8.6, 71.0)
Donor type			
MRD	12	1	91.7 (63.7, 98.3)
MUD	53	16	69.5 (57.7, 78.6)
CTP age group			
28 days to < 10 years	32	9	71.9 (56.4, 82.7)
10 years to < 18 years	33	8	75.3 (60.2, 85.4)
ICH age group			
28 days to 24 months	8	1	87.5 (50.0, 97.5)
2 to 11 years	25	8	68.0 (50.0, 80.7)
12 to 17 years	32	8	74.5 (59.0, 84.9)

*Rate at 36 months not available, therefore rate at end of documentation displayed.

GVHD-FREE AND RELAPSE/ PROGRESSION-FREE SURVIVAL



	Treosulfan
Number of subjects at risk	65
Events	28 (43.1%)
Censored	37 (56.9%)
Rate at 36 months[a] [%]	56.7
90% CI	(45.9, 66.1)

Note: „GvHD-free" defined as no acute GvHD of at least grade III and no moderate/severe chronic GvHD. „Chronic GvHD-free" defined as no moderate/severe chronic GvHD.

[a] Based on Kaplan-Meier estimates

AUTHORS' CONCLUSION

- Treosulfan-based conditioning with BSA-adapted dosing is safe and effective in pediatric patients with hematologic malignancies.
- Only a limited interindividual PK variability for Treosulfan was observed, the BSA-adapted dosing led to equivalent Treosulfan exposure in all dose groups.
- Treosulfan/Fludarabine/Thiotepa is a suitable myeloablative preparative treatment option for pediatric patients with hematologic malignancies.

alloHSCT - allogene hematopoietic stem cell transplantation
ALL - acute lymphoblastic leukemia
AML - acute myeloid leukemia
MDS - myelodysplastic syndrome
JMML - juvenile myelomonocytic leukemias
ICH - International Council of Harmonization
MSD - matched sibling donor
MFD - matched family donor
MRD - matched related donor
MUD - matched unrelated donor
UCB - umbilical cord blood
CI - confidence interval
RFS - relapse free survival
PFS - progression free survival
GvHD - graft-versus-host disease
PK - pharmacokinetic
EFS - event-free survival
TRM - transplant-related mortality
OS - overall survival

PEDIATRIC PATIENTS WITH NON-MALIGNANT DISEASES

RANDOMIZED PHASE II TRIAL: NON-MALIGNANT DISEASES[2,3]

Sykora KW, Beier R, Schulz A, Cesaro S, Greil J, Gozdzik J, Sedlacek P, Bader P, Schulte J, Zecca M, Locatelli F, Gruhn B, Reinhardt D, Styczynski J, Piras S, Fagioli F, Bonanomi S, Caniglia M, Li X, Baumgart J, Kehne J, Mielcarek-Siedziuk M, Kalwak K.

Hematopoietic stem cell transplantation (HSCT) is an effective treatment for patients with non-malignant diseases and for many is the only known cure.[4] The use of Treosulfan as part of conditioning for HSCT in pediatric patients is increasing for both malignant and non-malignant disorders and showed promising results in its pivotal trials in children.[1,3,5]

Trial design

DAYS	-7	-6	-5	-4	-3	-2	-1	0
TREOSULFAN i.v. (BSA adapted: 10, 12 or 14g/m²/day over 120min, prior to Fludarabine)		x	x	x				
OR								
BUSULFAN i.v. (3.2 to 4.8 mg/kg/day)	x	x	x	x				
Fludarabine i.v. (30 mg/m²/day)	x	x	x	x	x			
Thiotepa i.v (2 x 5mg/kg/day)						xx		
Allogeneic stem cell transplantation								x

*Thiotepa (2 × 5 mg/kg) could be added at investigator's discretion

[2]EU Clinical Trials Register. Clinical Trial Results: Clinical phase 2 trial to compare treosulfan-based conditioning therapy with busulfan-based conditioning prior to allogeneic haematopoietic stem cell transplantation (HSCT) in paediatric patients with non-malignant diseases.; 2022 [cited 2023 Feb 28]. Available from: URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-005508-33/results.

[3]Sykora KW, Beier R, Schulz A, Cesaro S, Greil J, Gozdzik J, Sedlacek P, Bader P, Schulte J, Zecca M, Locatelli F, Gruhn B, Reinhardt D, Styczynski J, Piras S, Fagioli F, Bonanomi S, Caniglia M, Li X, Baumgart J, Kehne J, Mielcarek-Siedziuk M, Kalwak K. Treosulfan vs busulfan conditioning for allogeneic bmt in children with nonmalignant disease: a randomized phase 2 trial. Bone Marrow Transplant. 2024 Jan;59(1):107-116. doi: 10.1038/s41409-023-02135-9

PRIMARY ENDPOINT

Freedom from transplantation (treatment)-related mortality day +100.

SECONDARY ENDPOINTS

Comparative exploratory analyses also included engraftment, primary or secondary graft failure, complete (≥ 95%) or mixed (≥ 20%) donor-type chimerism, transplantation-related mortality (TRM), overall survival (OS), acute and chronic graft versus host disease (GVHD), and GVHD-free survival.

AGE OF PATIENTS

28 days to 17 years

NUMBER OF PATIENTS

n=106 were randomized, n=101 (50 Bu; 51 Treo) were included in efficacy and safety analysis

DISEASE

Primary immunodeficiencies	n=51
Inborn errors metabolism	n=6
Hemoglobinopathies	n=34
Bone marrow failure syndromes	n=10

SEX

Male	n=67
Female	n=34

DONOR TYPE

MRD	n=31
MUD	n=70

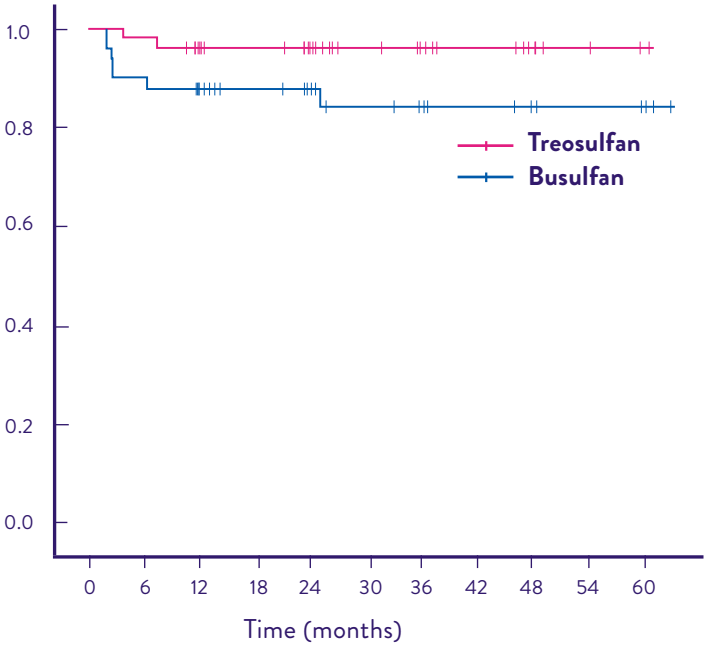
[4]Burroughs LM, Nemecek ER, Torgerson TR, Storer BE, Talano J-A, Domm J et al. Treosulfan-based conditioning and hematopoietic cell transplantation for nonmalignant diseases: a prospective multicenter trial. Biol Blood Marrow Transplant 2014; 20(12):1996–2003.

[5]Slatter MA, Rao K, Abd Hamid IJ, Nademi Z, Chiesa R, Elfeky R et al. Treosulfan and Fludarabine Conditioning for Hematopoietic Stem Cell Transplantation in Children with Primary Immunodeficiency: UK Experience. Biol Blood Marrow Transplant 2018; 24(3):529–36.

TRIAL OUTCOMES

- Freedom from TRM @ day +100 was 90.0% (95% CI: 78.2%, 96.7%) in the Busulfan- and 100.0% (95% CI: 93.0%, 100.0%) in the Treosulfan arm (P = 0.0528).
- Cumulative Incidence of Graft Failure was 15.8%(95% CI: 5.8%, 25.9%) for Treosulfan group versus 4.0 (95% CI: 0.0%, 9.4%) for Busulfan group respectively (P =0.0366).
- 12 months cGvHD-free survival 89.3% (95% CI: 76.2%, 95.4%) for Treosulfan vs 69.4% (95% CI: 54.4%, 80.3%) for Busulfan (p=0.0308).
- 12-months estimate of OS was 88.0% (95% CI: 75.2%, 94.4%) in the Busulfan arm versus 96.1% (95% CI: 85.2%, 99.0%) in the Treosulfan arm (HR: 0.29 [95% CI: 0.06, 1.41].

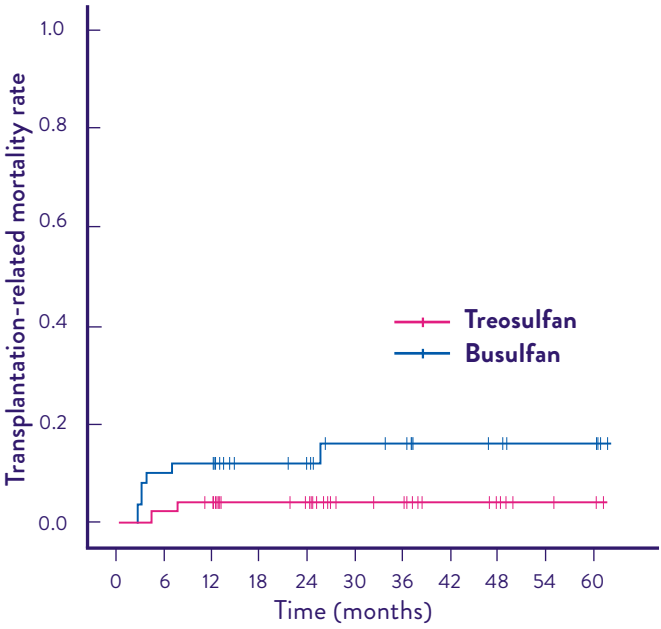
12 months OS



	Treosulfan	Busulfan
Number of subjects	51	50
Events	2 (3.9%)	7 (14.0%)
Censored	49 (96.1%)	43 (86.0%)
Rate at 12 months [%]	96.1	88.0
95% CI	(85.2, 99)	(75.2, 94.4)
Hazard Ratio [a]		0.29
95% CI		(0.06, 1.41)
p-value [a]		0.1244

[a] adjusted for Thiotepa and disease as factors using Cox regression model

12 months TRM



	Treosulfan	Busulfan
Number of subjects	51	50
Events	2 (3.9%)	7 (14.0%)
Censored	49 (96.1%)	43 (86.0%)
Rate at 12 months [%]	**3.9**	**12.0**
95% CI	**(1.0,14.8)**	**(5.6,24.8)**
Hazard Ratio [a]		0.29
95% CI		(0.06, 1.41)
p-value [a]		0.1244

[a] adjusted for Thiotepa and disease as factors using Cox regression model

SUMMARY

Children that underwent conditioning with Treosulfan had a higher overall survival despite the higher rate of graft failure. Children in the Treosulfan group had a lower rate of cGvHD compared to the Busulfan group. This study confirmed treosulfan to be an excellent alternative to busulfan and can be safely used for conditioning treatment in children with non-malignant disease.

TREOSULFAN-BASED CONDITIONING REGIMENS IN CHILDREN

- Resulted in high OS rates.
- BSA-adapted dosing: Therapeutic drug monitoring not required[1,6].

TRECONDI®-BASED THERAPY:

An effective and reduced toxicity conditioning regimen.

[1]Kalwak K, Mielcarek M, Patrick K, Styczynski J, Bader P, Corbacioglu S et al. Treosulfan-fludarabine-thiotepa-based conditioning treatment before allogeneic hematopoietic stem cell transplantation for pediatric patients with hematological malignancies. Bone Marrow Transplant 2020. Available from: URL: https://www.nature.com/articles/s41409-020-0869-6.pdf.

[6]Van der Stoep MYEC, Bertaina A, Moes DJAR, Algeri M, Bredius RGM, Smiers FJW et al. Impact of treosulfan exposure on early and long-term clinical outcome in pediatric allogeneic HSCT recipients: a prospective multicenter study. Transplantation and Cellular Therapy 2021.

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Trecondi® 1 g / 5 g powder for solution for infusion

Qualitative and quantitative composition: One vial Trecondi 1 g (5 g) powder for solution for infusion contains 1 g (5 g) of treosulfan. When reconstituted, 1 mL of the solution for infusion contains 50 mg treosulfan. **Therapeutic indications:** Treosulfan in combination with fludarabine is indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients and in paediatric patients older than one month with malignant and non-malignant diseases. **Posology and method of administration:** Administration should be supervised by a physician experienced in conditioning treatment followed by alloHSCT. *Adults with malignant disease:* Treosulfan is given in combination with fludarabine. Treosulfan 10 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (day -4, -3, -2) before stem cell infusion (day 0). The total treosulfan dose is 30 g/m²; Treosulfan should be administered before fludarabine. *Adults with non malignant disease*: Treosulfan is given in combination with fludarabine with or without thiotepa. Treosulfan 14 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (day -6, -5, -4) before stem cell infusion (day 0). The total treosulfan dose is 42 g/m²; Treosulfan should be administered before fludarabine. *Paediatric population:* Treosulfan is given in combination with fludarabine, with or without thiotepa. **Contraindications:** Hypersensitivity to the active substance; active non-controlled infectious disease; severe concomitant cardiac, lung, liver, and renal impairment; Fanconi anaemia and other DNA breakage repair disorders; pregnancy; administration of live vaccine. **Undesirable effects:** *Infections, infestations:* Very commonly infections (bacterial, viral, fungal). Commonly **s**epsis. Septic shock. *Neoplasms:* Treatment related second malignancy. *Blood, lymphatic system:* Very commonly myelosuppression, pancytopenia, febrile neutropenia. *Immune system:* Commonly hypersensitivity. *Metabolism and nutrition:* Commonly decreased appetite. Uncommonly glucose tolerance impaired including hyperglycaemia and hypoglycaemia. Acidosis, alkalosis, electrolyte imbalance, hypomagnesaemia. *Psychiatric:* Commonly insomnia. Uncommonly confusional state. *Nervous system:* Commonly headache, dizziness. Uncommonly intracranial haemorrhage, peripheral sensory neuropathy. Encephalopathy, intracranial haemorrhage, extrapyramidal disorder, syncope, paraesthesia, seizure. *Eye:* Dry eye, conjunctival haemorrhage. *Ear:* Uncommonly vertigo. *Cardiac:* Commonly cardiac arrhythmias (e.g. atrial fibrillation, sinus arrhythmia). Cardiac arrest, cardiac failure, myocardial infarction, pericardial effusion. *Vascular:* Commonly hypertension, hypotension, flushing. Uncommon haematoma. Embolism, capillary leak syndrome. *Respiratory, thoracic, mediastinal:* Commonly dyspnoea, epistaxis, oropharyngeal pain. Uncommonly pneumonitis, pleural effusion, pharyngeal or laryngeal inflammation, hiccups. Laryngeal pain, cough, dysphonia, hypoxia. *Gastrointestinal:* Very commonly stomatitis/mucositis, diarrhoea, nausea, vomiting, abdominal pain. Commonly oral pain, gastritis, dyspepsia, constipation, dysphagia, oesophageal or gastrointestinal pain, anal inflammation. Uncommonly mouth haemorrhage, abdominal distension, dry mouth. Gastric haemorrhage, neutropenic colitis, oesophagitis, proctitis, gingival pain. *Hepatobiliary:* Very commonly hepatotoxicity. Uncommonly veno-occlusive liver disease. Hepatomegaly. *Skin, subcutaneous tissue:* Very commonly pruritus, alopecia. Commonly (maculo-papular) rash, purpura, erythema, urticaria, palmar plantar erythrodysaesthesia syndrome, dermatitis exfoliative, pain of skin, skin hyperpigmentation. Uncommonly erythema multiforme, dermatitis acneiform, dry skin. Skin necrosis or ulcer, dermatitis, dermatitis bullous, dermatitis diaper. *Musculoskeletal and connective tissue:* Commonly pain in extremity, back pain, bone pain, arthralgia. Uncommonly myalgia. *Renal, urinary:* Commonly acute kidney injury, haematuria. Uncommonly urinary tract pain. Renal failure, haemorrhagic or noninfective cystitis, dysuria. *Reproductive system:* Scrotal erythema, penile pain. *General, administration site:* Very commonly asthenic conditions (fatigue, asthenia, lethargy), pyrexia. Commonly oedema, chills. Uncommonly non cardiac chest pain, pain, face oedema. *Investigations:* Very commonly blood bilirubin increased, ALT increased. Commonly AST increased, γGT increased, C-reactive protein increased, weight decreased, weight increased. Uncommonly blood alkaline phosphatase increased. Blood lactate dehydrogenase (LDH) increased. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 11/2023

Trecondi has been authorised in all countries of the EU as well as in Belarus, Iceland, Kazakhstan, Norway, Liechtenstein, Russia, Switzerland (Ideogen AG), United Kingdom, Ukraine

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W-PROM-000419/v2.0/04.2024

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