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Le cellule mesenchimali nella terapia della GVHD refrattaria del bambino

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Disclosure Giovanna Lucchini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

MSC 2026: a che punto siamo?

MSC approvate per aGVHD refrattaria a steroide in eta' pediatrica in

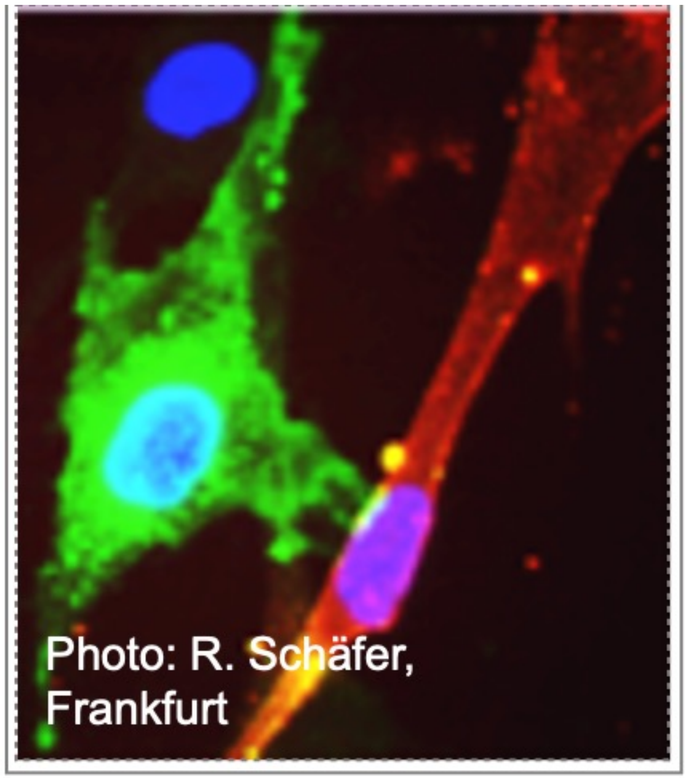
Canada (2012), Nuova Zelanda (2012), Giappone (2016), USA (2024)

British Society BMT GVHD revised guidelines

Overall, the complex biology of MSCs including variability in MSC donor, source, and manufacturing, coupled with variation in administration protocols and diverse patient characteristics, add to the challenges in comparing clinical trial outcomes, which are yet to demonstrate a clear benefit in patients with SR aGvHD

EBMT pediatric GVHD revised guidelines

In children and adolescents with grade II-IV acute GvHD refractory or intolerant to ruxolitinib,
as well as those with infectious comorbidities,
mesenchymal stromal cells (MSCs) may be considered



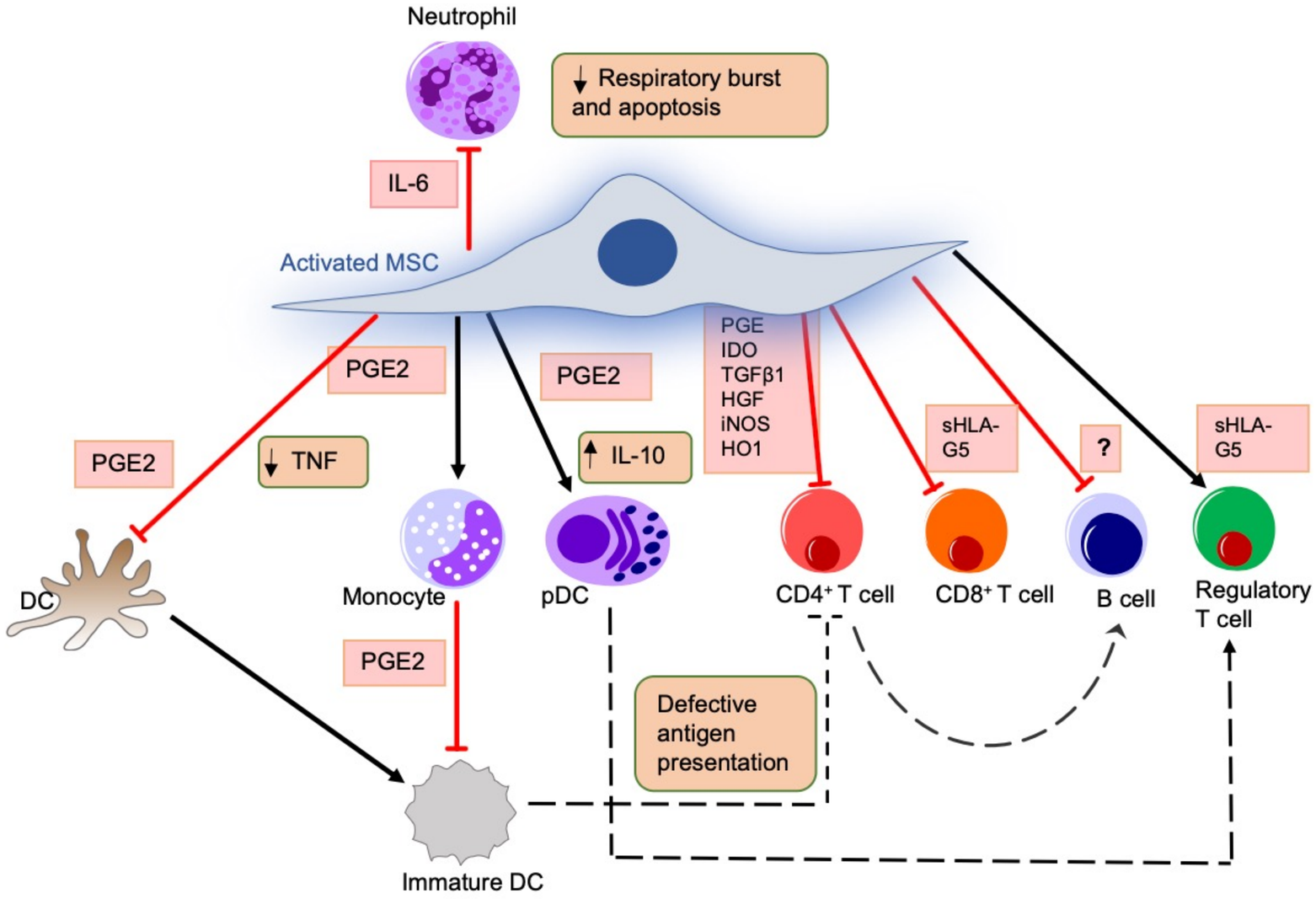
ISCT Mesenchymal and Tissue Stem Cell Committee

Table. Summary of Criteria to Identify Mesenchymal Stromal Cells (MSCs).

1. Adherence to plastic in standard culture conditions		
2. Phenotype	Positive (≥95% +)	Negative (<2% +)
	CD105	CD45
	CD73	CD34
	CD90	CD14 or CD11b
		CD79α or CD19
		HLA-DR
3. Differentiation: (by staining of in vitro cell culture)	Bone, Adipose, Cartilage	

Supporto all'ematopoiesi

Proprieta' immunomodulatorie paracrine



Adattato da Uccelli et al, Nature, 2006

Clinical Trial > Lancet. 2008 May 10;371(9624):1579-86.
doi: 10.1016/S0140-6736(08)60690-X.

Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study

Katarina Le Blanc [1], Francesco Frassoni, Lynne Ball, Franco Locatelli, Helene Roelofs, Ian Lewis, Edoardo Lanino, Berit Sundberg, Maria Ester Bernardo, Mats Remberger, Giorgio Dini, R Maarten Egeler, Andrea Bacigalupo, Willem Fibbe, Olle Ringdén; Developmental Committee of the European Group for Blood and Marrow Transplantation

Table 1

Characteristic	Value
Patients (Pediatric vs Adults)	Pediatric and adult patients (n = 55)
Grade of acute GVHD	Grade II–IV steroid-resistant acute GVHD
MSC median dose	1.4 × 10^6 cells/kg
Number of MSC infusions	1–5 infusions
Complete Response (CR)	30/55 (55%)
Partial Response (PR)	9/55 (16%)
Overall Survival (OS)	~53% vs 16% at 2 years CR vs NR

CTMO Monza-Bergamo

Platelet-lysate-expanded mesenchymal stromal cells as a salvage therapy for severe resistant graft-versus-host disease in a pediatric population.

Lucchini G, **Introna M**, Dander E, Rovelli A, Balduzzi A, Bonanomi S, Salvadè A, Capelli C, Belotti D, Gaipa G, Perseghin P, Vinci P, Lanino E, Chiusolo P, Orofino MG, Marktel S, Golay J, Rambaldi A, Biondi A, D'Amico G, Biagi E.

Biol Blood Marrow Transplant. 2010 Sep;16(9):1293-301. doi: 10.1016/j.bbmt.2010.03.017. Epub 2010

OR 71.4% of patients, CR in 23.8%

Mesenchymal stromal cells do not increase the risk of viral reactivation nor the severity of viral events in recipients of allogeneic stem cell transplantation.

Lucchini G, Dander E, Pavan F, Di Ceglie I, Balduzzi A, Perseghin P, Gaipa G, Algarotti A, **Introna M**, Rambaldi A, Rovelli A, Biondi A, Biagi E, D'Amico G.

Stem Cells Int. 2012;2012:690236. doi: 10.1155/2012/690236. Epub 2012 May 30.

No severe infections.

Immunological response to viral stimulus/virus specific T-cytotoxic activity.

Mesenchymal stromal cells for the treatment of graft-versus-host disease: understanding the in vivo biological effect through patient immune monitoring.

Dander E, **Lucchini G**, Vinci P, **Introna M**, Masciocchi F, Perseghin P, Balduzzi A, Bonanomi S, Longoni D, Gaipa G, Belotti D, Parma M, Algarotti A, Capelli C, Golay J, Rovelli A, Rambaldi A, Biondi A, Biagi E, D'Amico G.

Leukemia. 2012 Jul;26(7):1681-4. doi: 10.1038/leu.2011.384. Epub 2012 Jan 13.

Increased Tregs compared with Th1 and Th17 cells in MSC responders

Treatment of graft versus host disease with mesenchymal stromal cells: a phase I study on 40 adult and pediatric patients.

Introna M, **Lucchini G**, Dander E, Galimberti S, Rovelli A, Balduzzi A, Longoni D, Pavan F, Masciocchi F, Algarotti A, Micò C, Grassi A, Deola S, Cavattoni I, Gaipa G, Belotti D, Perseghin P, Parma M, Pogliani E, Golay J, Pedrini O, Capelli C, Cortelazzo S, D'Amico G, Biondi A, Rambaldi A, Biagi E.

Biol Blood Marrow Transplant. 2014 Mar;20(3):375-81. doi: 10.1016/j.bbmt.2013.11.033. Epub 2013

OR at 28 days 67.5%, with 27.5% CR.

Grade II GVHD better (61.5% vs 11.1%, P = .002) and better in children(46.7 vs 16.0%, P = .065).

Studi che comprendano almeno 15 pz pediatrici

Resnik et al, 2014	25 bambini	CR34% OR66%
Ball et al, 2013	37 bambini	CR65% PR 22%
Bader et al, 2018	51 bambini	CR32% PR 51%
Dottoli et al, 2017	16 bambini	CR6% PR 43%
Kurtzberg et al, 2020	241 bambini	CR14% PR 51%
Kurtzberg et al, 2020	54 bambini	CR30%

Fonti

Terreni di coltura

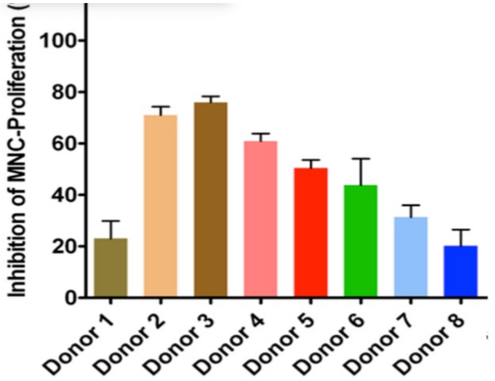
Passaggi in coltura

Compatibilita’ D/R

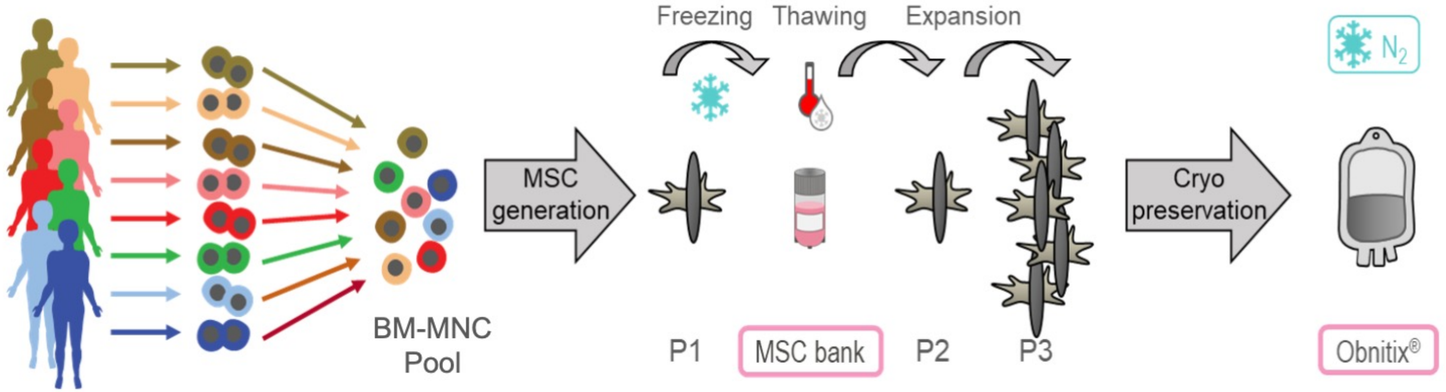
Dosi

Schema di infusione

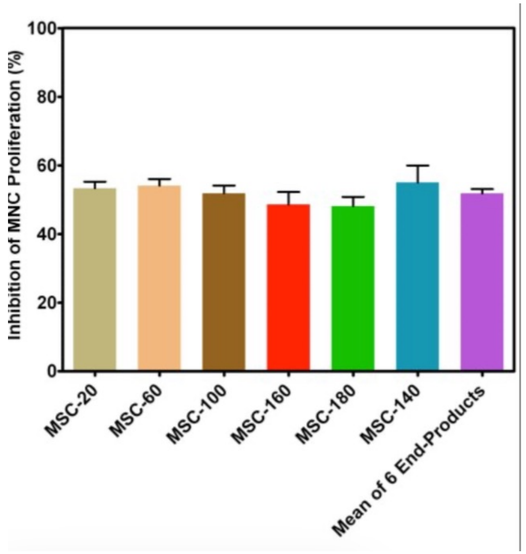
Limitare la differenza biologica intrinseca del donatore



Kuci et al, Haematologica 2016



- Cell product of human mesenchymal stromal cells (MSC)
- Generated from pooled bone marrow mononuclear cells (BM-MNC) of eight third-party donors
- Approved for the clinical treatment of steroid refractory GvHD (PEI.A.11748.01.1)

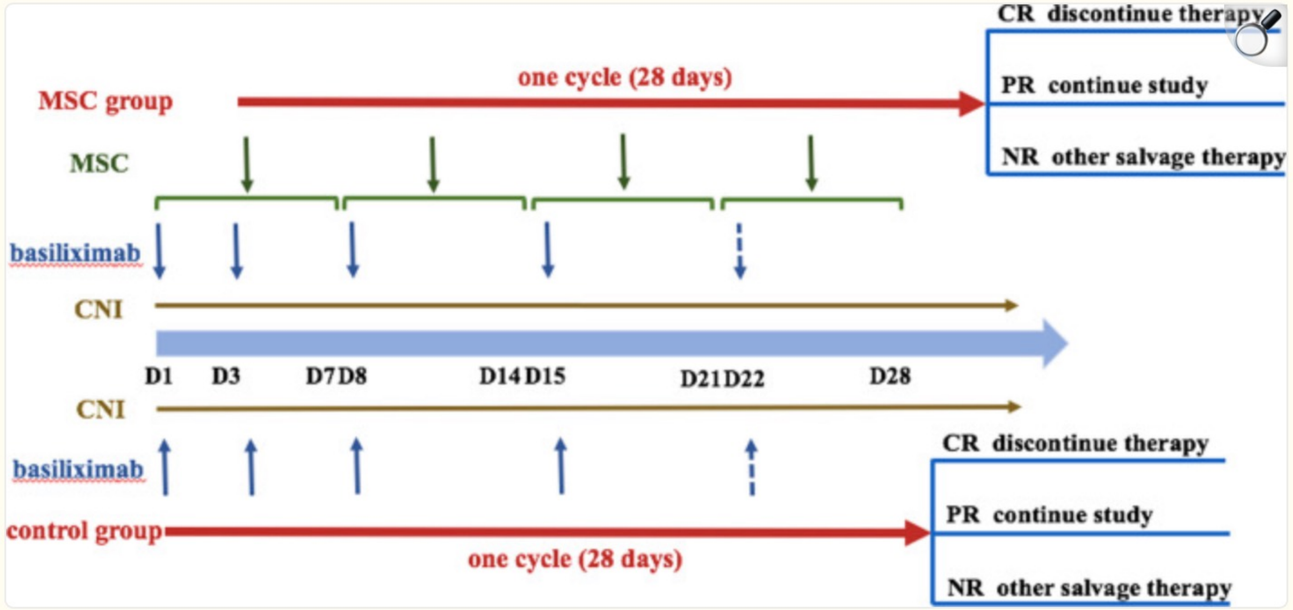


Random: NCT00366145, Kebriaei et al, BBMT 2020

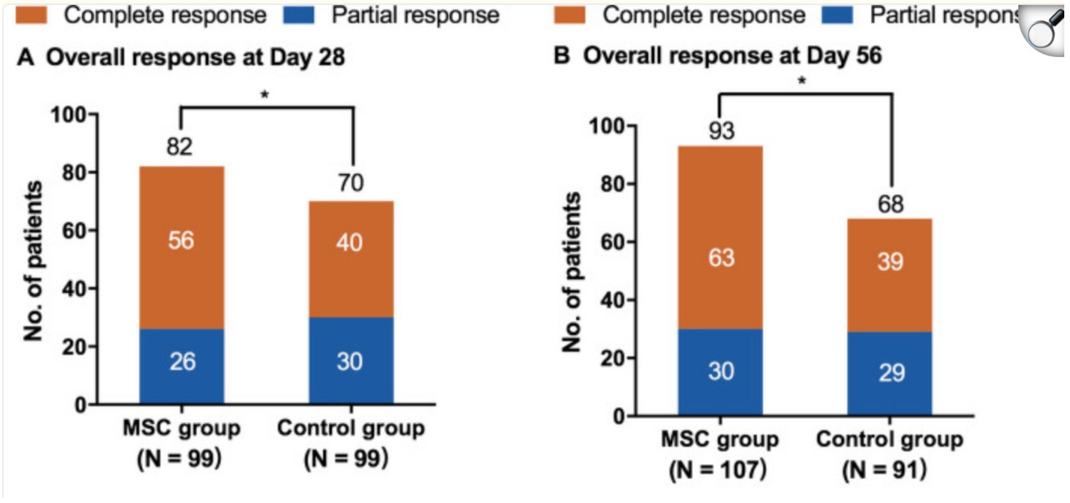
	Durable Complete Response, n (%) [95% CI]		Overall Response, n (%) [95% CI]	
Characteristic	Remestemcel-L	Placebo	Remestemcel-L	Placebo
Overall	60/163 (36.8)	26/81 (32.1)	95/163 (58.3)	44/81 (54.3)
	[29.4-44.7]	[22.2-43.4]	[50.3-65.9]	[42.9-65.4]
Age				
<18	9/14 (64.3)	6/13 (46.2)	9/14 (64.3)	3/13 (23.1)*
	[35.1-87.2]	[19.2-74.9]	[35.1-87.2]	[5.0-53.8]
≥18	51/149 (34.2)	20/68 (29.4)	86/149 (57.7)	41/68 (60.3)
	[26.7-42.4]	[19.0-41.7]	[49.4-65.8]	[47.7-72.0]

- **Study Design:** Phase III randomized trial (2006–2009) including 260 patients with acute GvHD (aGVHD), randomized 2:1 to receive MSCs or placebo plus standard second-line therapy.
- **Treatment Regimen:** Patients received 8 intravenous infusions over 4 weeks; randomization stratified by aGVHD severity grade.
- **Primary Endpoint:** MSCs did not significantly improve durable complete response compared with placebo (35% vs 30%; p=0.42).
- **High-Risk Patients:** Significant improvement in day-28 OR in severe aGVHD grades C/D with MSCs (58% vs 37%; p=0.03).
- **Pediatric Benefit:** Pediatric patients showed markedly higher response rates (64% vs 23%; p=0.05).
- **Conclusion:** Primary endpoint not met but promising efficacy in high-risk and pediatric subgroups.

Zhao K, et al. Mesenchymal stromal cells plus basiliximab, calcineurin inhibitor as treatment of steroid-resistant acute graft-versus-host d



Variable	MSC group No. (%)	Control group No. (%)
No. of patients	99	99
Age, median (range), years	28 (16–59)	29 (16–57)
< 18 year	14	17
≥ 18 year	85	82



- The OR at day 28 was higher in the MSC group than the control group (82.8% vs. 70.7% *P* = 0.043).
- The durable OR at day 56 was higher in the MSC group (78.8% vs. 64.6% *P* = 0.027).
- The median failure-free survival was longer in the MSC group (11.3 vs. 6.0 months; *P* = 0.024).
- The 2-year cumulative incidence of cGVHD was 39.5% and 62.7% in the MSC and control groups (*P* = 0.005).

Random: HOVON113, Oosten et al, Haemasphere 2022

- **Study Design:** Randomized, placebo-controlled trial evaluating intravenous MSC infusions + standard MMF therapy in SrGVHD
- **Patients:** 41 patients **(7 children)** enrolled across 5 European countries. Most had severe disease (68% grade III, 20% grade IV).
- **Primary Outcome:** Day-28 OR was higher with MSCs (60%) vs placebo (38%), but not statistically significant (p=0.19).
- **Survival & Safety:** 1-year OS was higher with MSCs (45% vs 33%), with similar infectious complications and no infusion toxicity.
- **Study Limitation:** Trial closed early due to regulatory and recruitment issues, resulting in insufficient power to confirm efficacy.
- **Conclusion:** MSC treatment showed a favorable trend but no statistically significant improvement in response.

Clinical Development Programme of the Innovative Mesenchymal Stromal Cell Product MSC-FFM/MC0518 for Steroid-Refractory Acute Graft-Versus-Host Disease: Design of 2 Randomised Controlled Trials in Adult and Paediatric Patients

Robert Zeiser[a] Halvard Bönig[b,c] Elena Osswald[d] Uwe Pichlmeier[d]
Ann-Kristin Möller[d] Michael Tribanek[d] Maria Lazarou-Wild[d]
Renate von der Weth[d] Lisa-Marie Pfeffermann[c] Peter Bader[e]

Aiming to recruit 48 pts, 36 sites,

5 EU countries

Recruitment completed

end of January 2026

Data analysis awaited.