Inyección intra-arterial de células mononucleadas autólogas de médula ósea en el ictus isquémico. Ensayo clínico fase IIb multicéntrico randomizado y controlado (IBIS trial).

F. Moniche, J.A. Cabezas-Rodriguez, R. Valverde, L. Lebrato-Hernandez, B. Pardo-Galiana, L. Ainz, M. Medina-Rodriguez, I. Escudero-Martinez, V. Escamilla-Gomez, J. Ortega-Quintanilla, E. Zapata-Arriaza, J. De la Torre, M.A. Gamero, S. Perez, R. Espinosa-Rosso, L. Forero-Diaz, M. Moya, P. Piñero, C. Calderón-Cabrera, C. Herrera, F. Delgado, J.-J. Ochoa-Sepúlveda, A. Gonzalez, J. Montaner, IBIS trial Investigators Group.

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RICORS-ICTUS
Instituto de Salud Carlos III

DECLARACIÓN DE CONFLICTO DE INTERESES

Inyección intra-arterial de células mononucleadas autólogas de médula ósea en el ictus isquémico. Ensayo clínico fase IIb multicéntrico randomizado y controlado (IBIS trial).

Respecto a esta comunicación existen las siguientes relaciones que podrían ser percibidas como potenciales conflictos de intereses: **NO EXISTEN CONFLICTOS DE INTERÉS**

La comunicación que presento NO ha sido financiada, total o parcialmente, por ninguna empresa con intereses económicos en los productos, equipos o similares citados en la misma.

La comunicación que presento **ha sido financiada por las siguientes becas:**
PI15/01197, PI18/01414, PIC18/00016 y RD16/0019/0015, RD21/0006/0015 del Ministerio de Economía y Competitividad, cofinanciado por el ISCIII y los fondos FEDER; beca de la Fundación Mutua Madrileña.

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UNIÓN EUROPEA
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"Una manera de hacer Europa"

Introducción

- Incluso con los tratamientos de recanalización, el ictus es la 1ª causa de discapacidad.
- **La terapia celular** es una opción terapéutica potencial, mediante la secreción de **citoquinas y factores de crecimiento que estimulan la plasticidad cerebral**
- Un ensayo clínico reciente fase II mostró datos **preliminares de eficacia** en ictus isquémico[1]
- **El trasplante intra-arterial de BM-MNC** ha demonstrado la seguridad en pacientes con ictus y la eficacia en modelos animales de ictus isquémico [2]
- Existe evidencia incipiente a favor de que una mayor dosis celular podría ser más eficaz.

[1]Hess et al. Lancet Neurol 2017. [2]Jeong, et al. Int J Stem Cells. 2014 [2]Moniche, et al. Stroke 2012

Protocol

Intra-arterial bone marrow mononuclear cells (BM-MNCs) transplantation in acute ischemic stroke (IBIS trial): protocol of a phase II, randomized, dose-finding, controlled multicenter trial

IBIS trial

- ✓ Multicentric randomized controlled single-blinded (outcomes assessor) clinical trial phase IIb
- ✓ Autologous BM-MNC intra-arterial injection
- ✓ Randomized 2:1:1 control vs two different doses BM-MNC ($2x10^6$/kg or $5x10^6$/kg)
- ✓ Sample size: total sample size of 76 patients provides 80% power to detect a difference of 18% in dependency in mRS

Promotor: Red Andaluza de Diseño y Traslación de Terapias Avanzadas - Fundación Pública Andaluza Progreso y Salud

ClinicalTrials.gov Identifier: NCT02178657
Nº EudraCT: 2013-002135-15

Moniche et al. Int J Stroke. 2015 Jun 4

Protocol

Intra-arterial bone marrow mononuclear cells (BM-MNCs) transplantation in acute ischemic stroke (IBIS trial): protocol of a phase II, randomized, dose-finding, controlled multicenter trial

IBIS trial

Inclusion criteria:

- ✓Ischemic MCA stroke patients within 1-7 days from stroke onset
- ✓Acute MCA non-lacunar ischemic lesions demonstrated in DWI-MRI
- ✓Age 18–80 years
- ✓ NIHSS 6-20
- ✓ Ipsilateral MCA permeability
- ✓Pre-stroke Modified Rankin Score <2

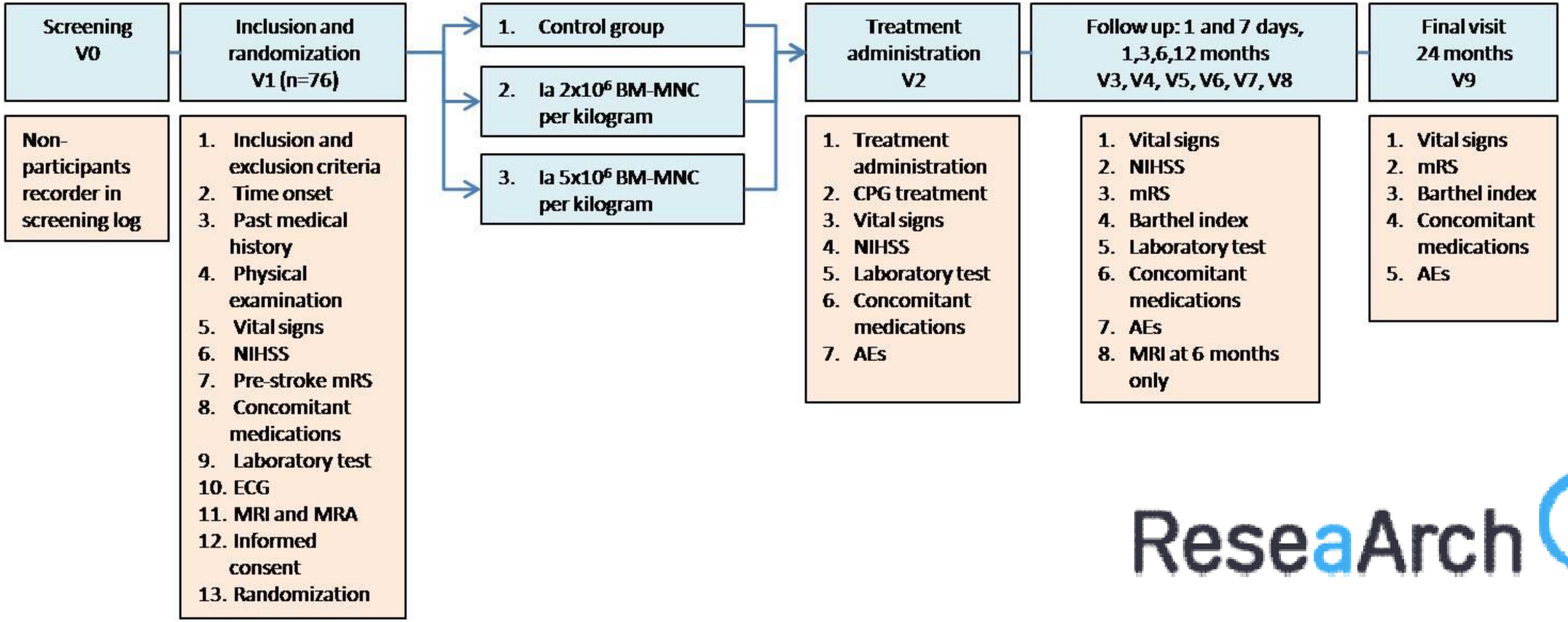
2. CENTROS PARTICIPANTES

Hospital Universitario Virgen del Rocío **Dr. Francisco Moniche**
Hospital Universitario Reina Sofía **Dr. Roberto Valverde**
Hospital Universitario Virgen Macarena **Dr. Miguel Ángel Gamero**
Hospital Universitario Puerta del Mar **Dr. Raúl Espinosa**

Moniche et al. Int J Stroke. 2015 Jun 4

Clinical trial flowchart

IBIS trial



ReseaArch

CRO externa

FDA 21 CRF part 11
Compliance certificate
ReseaArch®

✓ Status: recruitment completed

IBIS trial

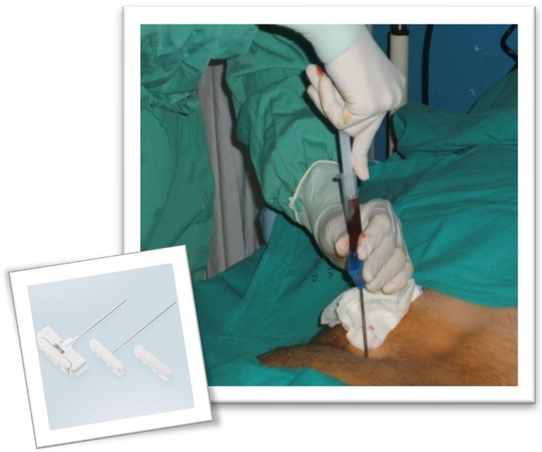
OBJETIVO PRIMARIO

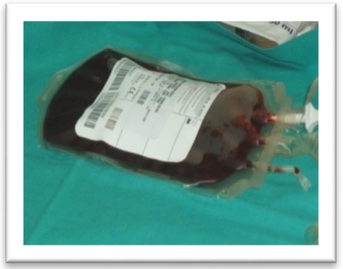
- Proporción de pacientes con escala de Rankin de 0-2 a los 6 meses, realizado por un evaluador ciego

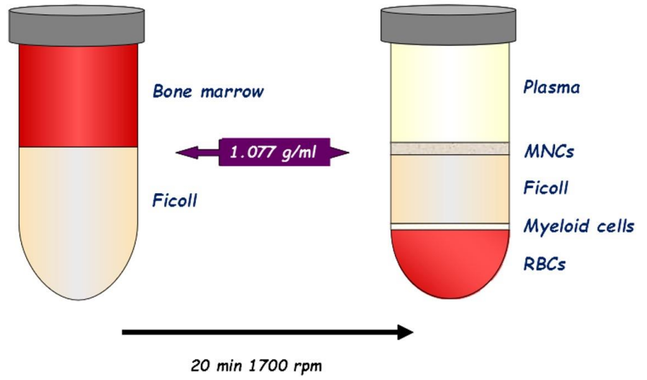
OBJETIVOS SECUNDARIOS

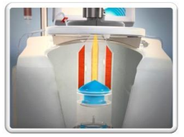
- Shift-analysis del mRS
- mRS 0-3 a los 6 meses; mRS 0-2 a 3 meses
- Diferencia en NIHSS y Barthel a 3 y 6 meses
- Evaluación de seguridad: % de SAEs, mortalidad

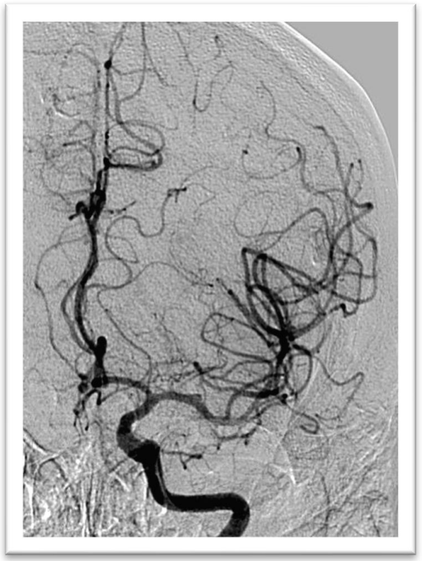
IBIS trial





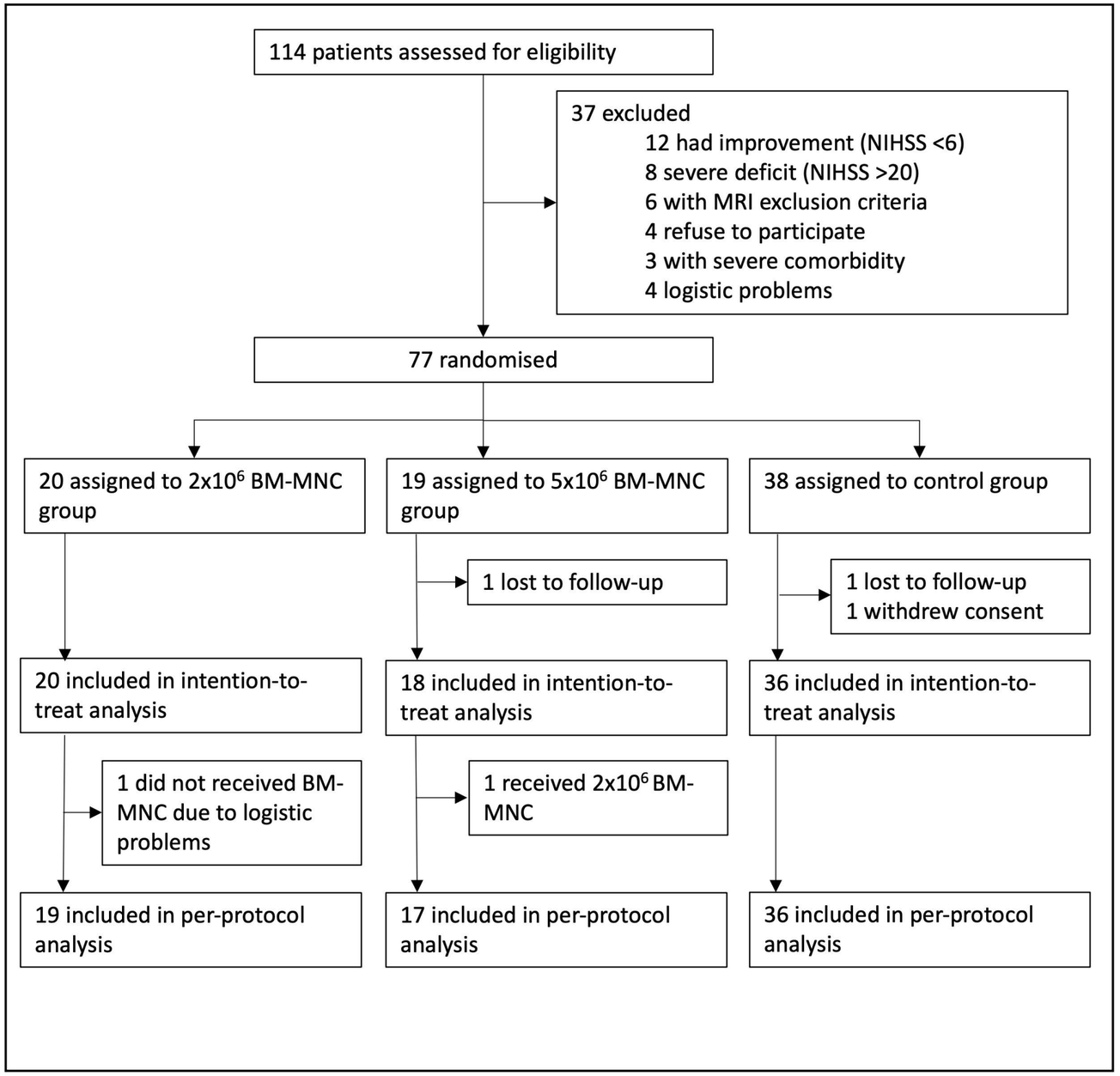






Moniche et al. Int J Stroke. 2015;10:1149-52

IBIS trial


114 patients assessed for eligibility
37 excluded
12 had improvement (NIHSS <6)
8 severe deficit (NIHSS >20)
6 with MRI exclusion criteria
4 refuse to participate
3 with severe comorbidity
4 logistic problems
77 randomised
20 assigned to 2x10^6 BM-MNC group
19 assigned to 5x10^6 BM-MNC group
38 assigned to control group
1 lost to follow-up
1 lost to follow-up
1 withdrew consent
20 included in intention-to-treat analysis
18 included in intention-to-treat analysis
36 included in intention-to-treat analysis
1 did not received BM-MNC due to logistic problems
1 received 2x10^6 BM-MNC
19 included in per-protocol analysis
17 included in per-protocol analysis
36 included in per-protocol analysis

BASAL CHARACTERISTICS

IBIS trial

	2mill/kg BM-MNC group (n=20)	5mill/kg BM-MNC group (n=19)	Control group (n=38)	p
Age (years)	62·6 (10·9)	63·2 (13·1)	62·3 (13·7)	0·92
Sex (Men)	11 (55%)	10 (52·6%)	25 (65·8%)	0·50
Vascular risk factors				
Hypertension	14 (70%)	10 (52·6%)	23 (60·5%)	0·54
Diabetes	3 (15%)	5 (26·3%)	9 (23·7%)	0·66
Dyslipidemia	4 (20%)	7 (36·8%)	20 (52·6%)	0·05
Atrial fibrillation	3 (15%)	6 (31·6%)	9 (23·7%)	0·47
Current smoker	5 (25%)	5 (26·3%)	9 (23·7%)	0·98
Ischemic cardiopathy	1 (5%)	1 (5·3%)	4 (10·5%)	0·68
Previous stroke	1 (5%)	0	2 (5·3%)	0·59
Stroke characteristics				
IV thrombolysis	10 (50%)	9 (47·4%)	16 (42·1%)	0·83
Mechanical thrombectomy	16 (80%)	14 (73·7%)	33 (86·8%)	0·46
TOAST etiology				0·17
Atherosclerotic	8 (40%)	5 (26·3%)	12 (32·4%)	
Cardioembolic	8 (40%)	10 (52·6%)	23 (62·2%)	
Cryptogenic	2 (10%)	4 (21·1%)	1 (2·7%)	
Other etiology	2 (10%)	0	1 (2·7%)	

BASAL CHARACTERISTICS

IBIS trial

	2mill/kg BM-MNC group (n=20)	5mill/kg BM-MNC group (n=19)	Control group (n=38)	p
Baseline NIHSS score (at inclusion)	12·4 (4·4)	12·7 (3·4)	12·3 (4·5)	0·94
Left MCA	13 (65%)	15 (78·9%)	27 (71·1%)	0·63
Aphasia	14 (70%)	15 (78·9%)	25 (69·4%)	0·83
Time from stroke to inclusion (days)	3·3 (1·1)	3·2 (1·6)	3·3 (1·1)	0·85
Time from stroke to BM injection (days)	5·7 (1·1)	5·5 (1·8)	-	0·83

SAFETY OUTCOMES

IBIS trial

	Low-dose BMMNC group (n=20)	High-dose BMMNC group (n=19)	Control group (n=38)
Patients with any adverse events	17 (85%; 70–100)	18 (95%; 84–100)	35 (92%; 81–100)
Patients with any serious adverse events*	5 (25%; 10–45)	9 (47%; 26–68)	14 (37%; 23–53)
Deaths†	0	2 (10%; 0–26)	3 (8%; 0–18)
Patients with anticipated treatment-related adverse events‡	2 (10%; 0–26%)	0	0
Patients with any related treatment-related serious adverse events	0	0	0

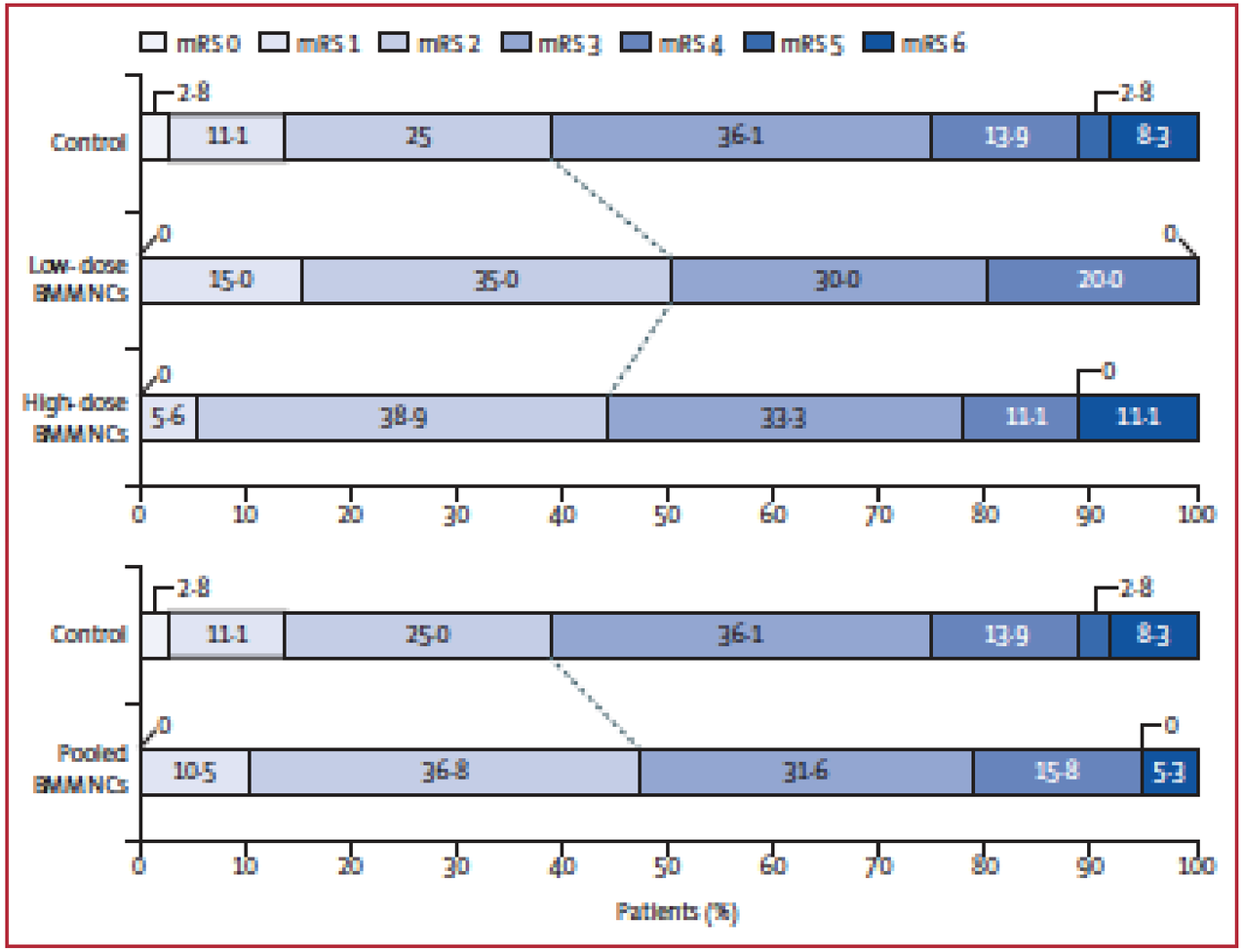
- ✓ No serious adverse events (SAE) were related to the cell therapy
- ✓ Two patients had minor femoral hematoma after intra-arterial injection of cells

PRIMARY OUTCOME

IBIS trial

	BM-MNC group (n=38)	Control group (n=36)	Adjusted OR	p
mRS 0-2 at 6 months	18 (**47.4%**)	11 (**38.9%**)	**2.22 (0.72-6.84)**	**0.16**

Low-dose BMMNC group vs control group		High-dose BMMNC group vs control group		Pooled BMMNC group vs control group	
Adjusted OR (95% CI) or β (95% CI)	p value	Adjusted OR (95% CI) or β (95% CI)*	p value	Adjusted OR (95% CI) or β (95% CI)*	p value
2·08 (0·55 to 7·85)	0·28	1·89 (0·52 to 6·96)	0·33	2·22 (0·72 to 6·85)	0·16



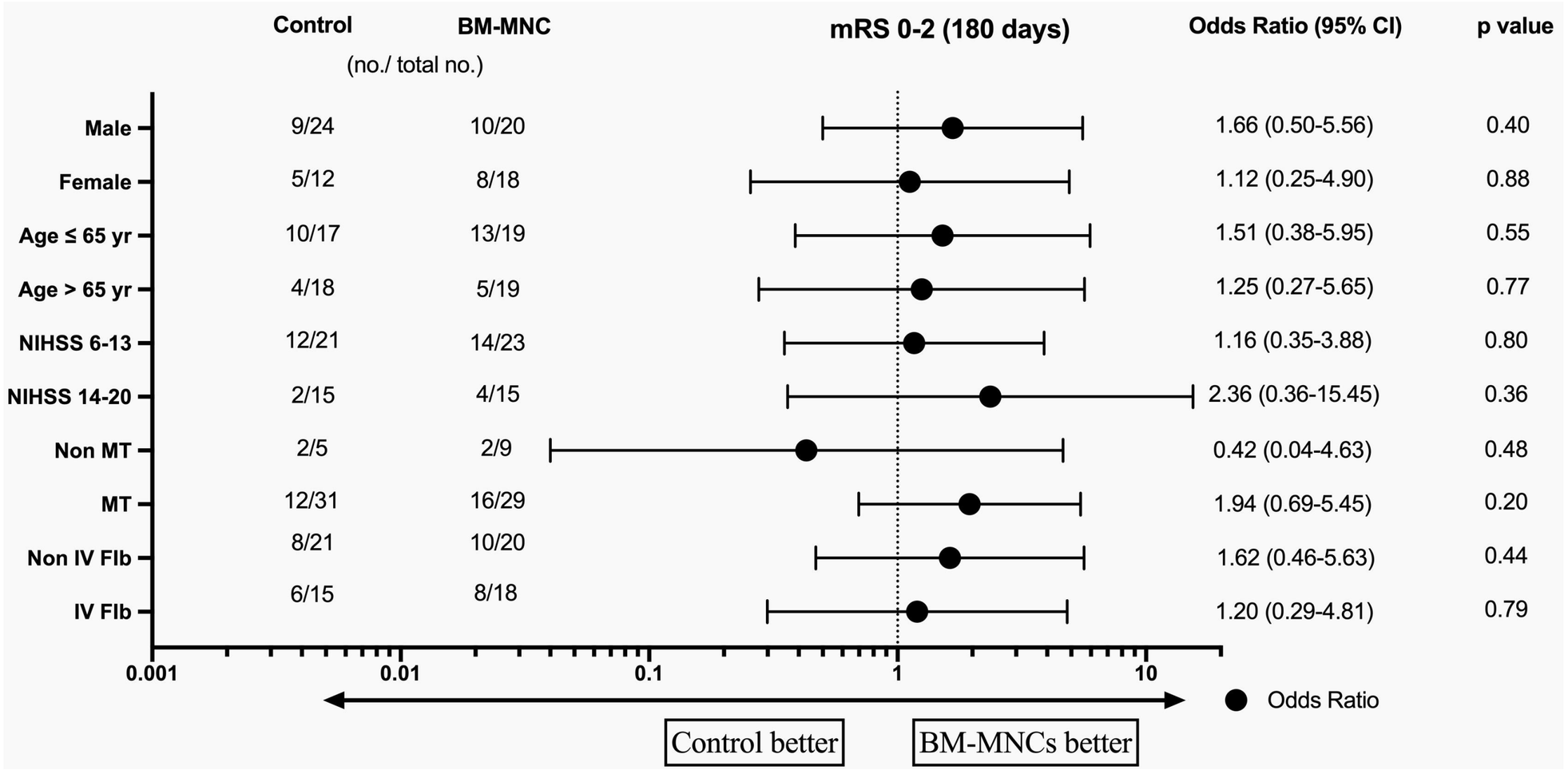
SECONDARY OUTCOMES

IBIS trial

	Low-dose BMMNC group (n=20)	High-dose BMMNC group (n=18)	Pooled BMMNC group (n=38)	Control group (n=36)	Low-dose BMMNC group vs control group		High-dose BMMNC group vs control group		Pooled BMMNC group vs control group	
					Adjusted OR (95% CI) or β (95% CI)	p value	Adjusted OR (95% CI) or β (95% CI)*	p value	Adjusted OR (95% CI) or β (95% CI)*	p value
mRS score of 0–3 at 6 months	16 (80%)	14 (77·8%)	30 (78·9%)	27 (75%)	1·34 (0·31–5·77)	0·69	1·26 (0·31 to 5·17)	0·75	1·30 (0·40 to 4·20)	0·66
Shift analysis mRS at 6 months*	..	..	..	..	1·80 (0·66 to 4·91)	0·25	1·40 (0·49 to 4·00)	0·53	1·65 (0·70 to 3·86)	0·25
NIHSS score at 6 months	4 (2 to 8)	7 (3 to 8)	5 (2 to 8)	4 (3 to 8)	−0·19 (−3·56 to 0·36)	0·11	0·05 (−2·07 to 3·07)	0·70	−0·07 (−2·56 to 1·26)	0·49
NIHSS score at 3 months	5 (2 to 8)	7 (2 to 10)	6 (2 to 8)	7 (2 to 10)	−1·44 (−3·13 to 0·52)	0·16	0·15 (−2·24 to 2·56)	0·89	−0·73 (−2·46 to 1·14)	0·46
Barthel index score >90 at 6 months	9 (45%)	3 (20%)	12 (34%)	9 (27%)	3·24 (0·78 to 13·42)	0·10	1·12 (0·21 to 5·83)	0·89	2·32 (0·66 to 8·13)	0·19
Barthel index score >90 at 3 months	8 (42%)	6 (37%)	14 (40%)	7 (21%)	4·91 (0·99 to 24·40)	0·05	5·56 (0·98 to 31·53)	0·05	5·55 (1·31 to 22·43)	0·02
Infarct volume change on MRI from baseline to 6 months, mL†	18·5 (5 to 42)	20·5 (11 to 32)	19·5 (8 to 35)	24 (13 to 47)	−0·17 (−19 to 5·6)	0·27	−0·13 (−15·6 to 6·6)	0·42	−0·17 (−15·6 to 3·6)	0·21
Post hoc efficacy outcomes										
mRS score of 0–2 at 3 months	11 (55%)	7 (39%)	18 (47%)	11 (32%)	4·46 (1·04 to 19·10)	0·04	2·97 (0·66 to 13·27)	0·15	3·72 (1·06 to 13·02)	0·04
Shift analysis mRS at 3 months*	..	..	..	..	2·32 (0·84 to 6·43)	0·10	1·67 (0·58 to 4·81)	0·34	2·01 (0·85 to 4·72)	0·11

IBIS trial

SUBGROUP ANALYSIS OF PRIMARY ENDPOINT



Safety and efficacy of intra-arterial bone marrow mononuclear cell transplantation in patients with acute ischaemic stroke in Spain (IBIS trial): a phase 2, randomised, open-label, standard-of-care controlled, multicentre trial

Francisco Moniche, Juan Antonio Cabezas-Rodriguez, Roberto Valverde, Irene Escudero-Martinez, Lucia Lebrato-Hernandez, Blanca Pardo-Galiana, Leire Ainz, Manuel Medina-Rodriguez, Javier de la Torre, Virginia Escamilla-Gomez, Joaquin Ortega-Quintanilla, Elena Zapata-Arriaza, Asier de Albóniga-Chindurza, Fernando Mancha, Miguel-Angel Gamero, Soledad Perez, Raul Espinosa-Rosso, Lucia Forero-Diaz, Miguel Moya, Pilar Piñero, Cristina Calderón-Cabrera, Sonia Nogueras, Rosario Jimenez, Vanesa Martin, Fernando Delgado, Juan-José Ochoa-Sepúlveda, Blanca Quijano, Rosario Mata, Monica Santos-González, Gloria Carmona-Sanchez, Concha Herrera, Alejandro Gonzalez, Joan Montaner

selectively target cells within the injured brain. However, intravenous delivery is also promising, as many animal studies have shown that cell delivery to the brain is not necessary to induce positive biological effects in the brain.[5] Whether intra-arterial delivery proves superior to intravenous or other delivery routes remains unknown. Overall, this trial advances the field of cell therapy for stroke in a positive direction and I look forward to Moniche and colleagues' next study.

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Department of Neurology, Institute for Stroke and Cerebrovascular Disease, University of Texas Health Science Center, Houston 77042, TX, USA

Moniche et al. Lancet Neurol 2023; 22: 137–46.

Desarrollo línea terapia celular en ictus

Fase I/II
Seguridad y viabilidad inyección intra-arterial CMN-MO en ictus

Finalizado 2012[1]

Pooling data
Evaluación seguridad y dosis eficaz

Finalizado 2016[2]

Fase IIb
Eficacia y seguridad inyección intra-arterial dos dosis CMN-MO en ictus

Finalizado 2023[3]

Subestudio BIOMARCADORES

Subestudio RM + DTI

AMASCIS-02 Fase IIb
Eficacia y seguridad inyección iv MSC alogénicas en ictus[4]

Fase III
Eficacia inyección intra-arterial CMN-MO en ictus

2023-¿?

[1] Moniche, et al. Stroke 2012; 43:2242-2244.
[2] Moniche, et al. Stem Cells Int. 2016;2016:8657173
[3] Moniche et al. Lancet Neurol 2023; 22: 137–46
[4] BMJ Open. 2021 Aug 9;11(8):e051790

Conclusiones

IBIS trial

- ✓Este es el **mayor ensayo realizado con terapia celular intra-arterial en ictus** y el **primero en evaluar dos dosis**.
- ✓En la era de la trombectomía, el tratamiento intra-arterial con BM-MNCs en ictus isquémico agudo fue seguro y bien tolerado
- ✓**No hubo mejorías significativas en el mRS a 6 meses** (endpoint primario)
- ✓Algunos **resultados positivos en endpoint secundarios (mRS a 3 meses)** garantiza el realizar nuevos ensayos.
- ✓Los datos no muestran claras diferencias de eficacia con un aumento de dosis celular.

Hospital Universitario Virgen del Rocío

IBiS INSTITUTODEBIOMEDICINADESEVILLA

IBIS trial

HUVM Hospital Universitario Virgen Macarena

HURS Hospital Universitario Reina Sofía

Hospital Universitario Puerta del Mar

¡Muchas gracias!