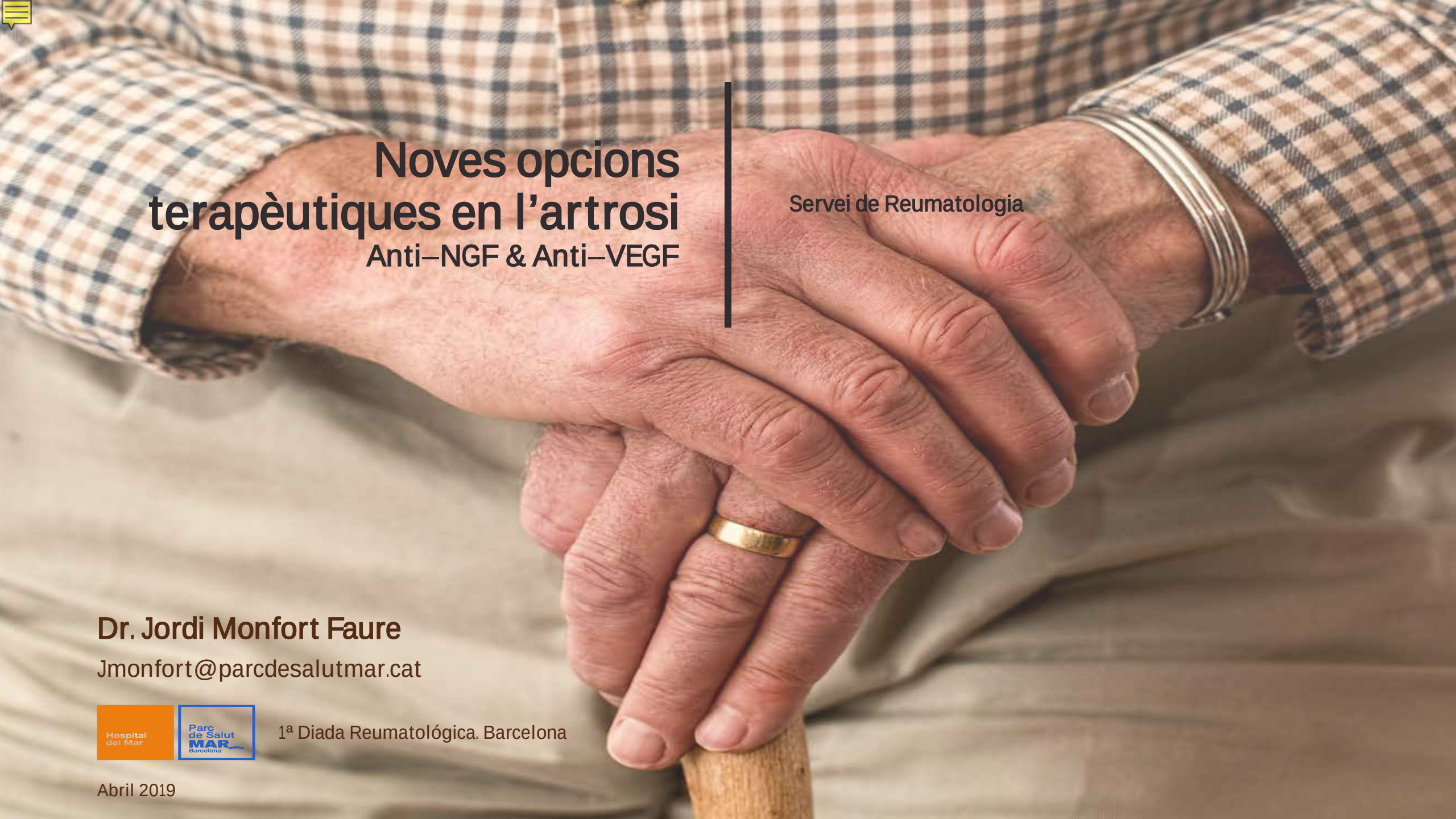


Noves opcions terapèutiques en l'artrosi

Anti–NGF & Anti–VEGF

Servei de Reumatologia

Dr. Jordi Monfort Faure

Jmonfort@parcdesalutmar.cat

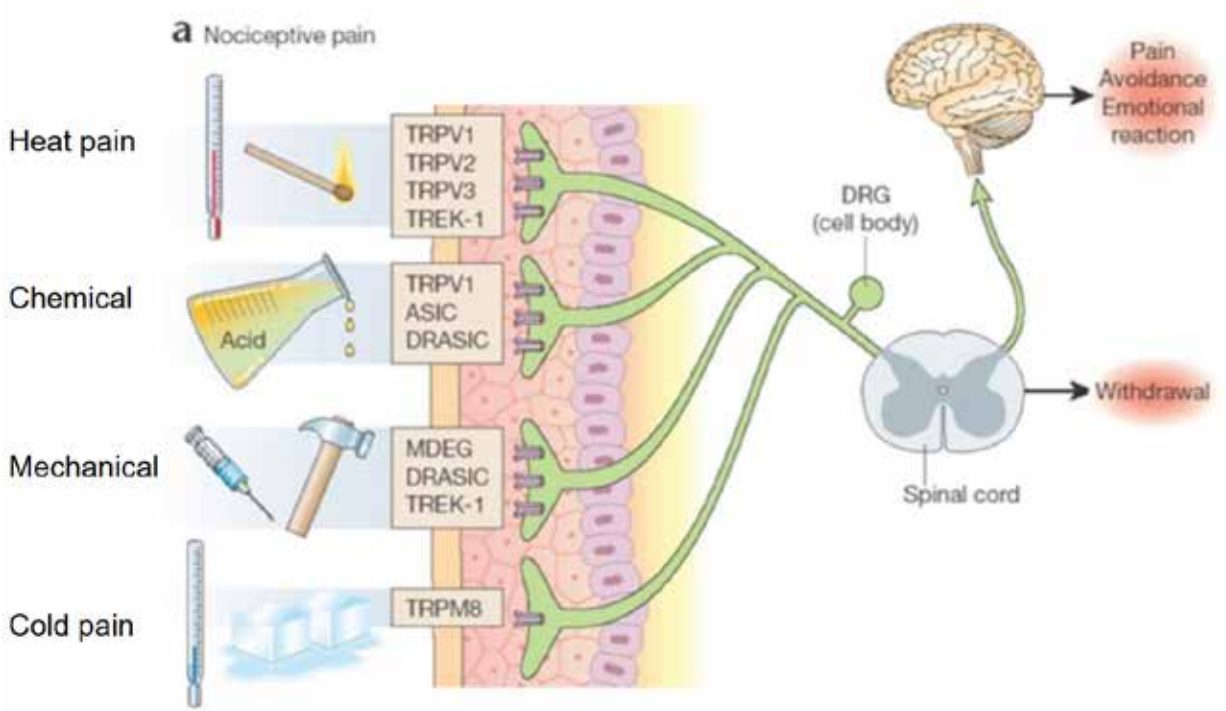
1ª Diada Reumatológica. Barcelona

Abril 2019

Fisiopatología

Servei de Reumatologia
Hospital del **MAR**

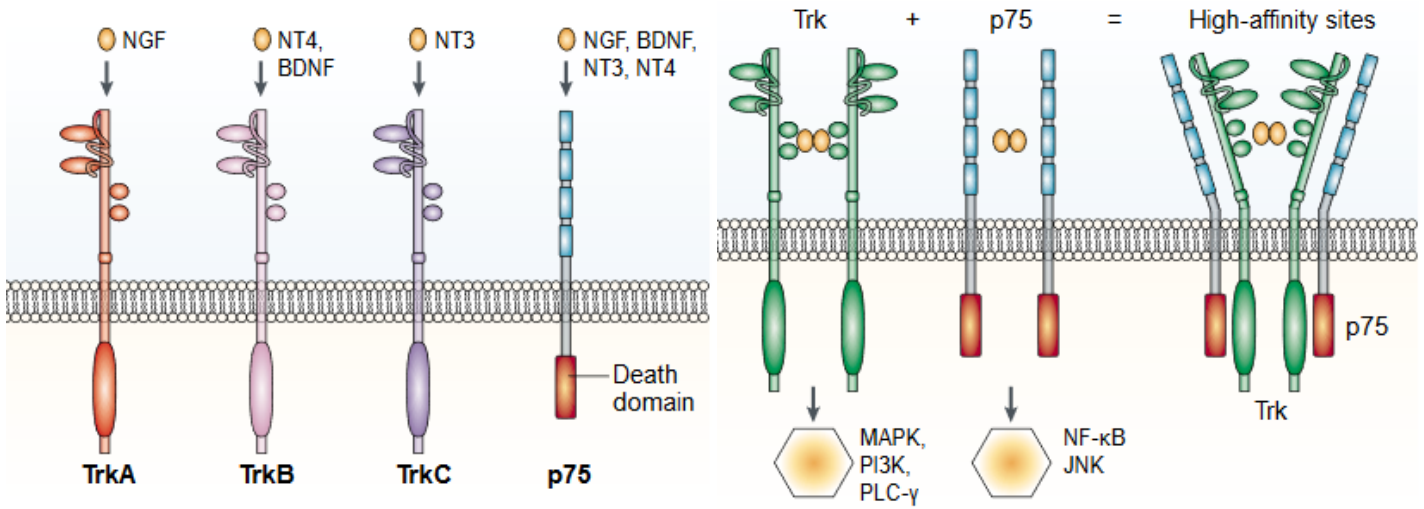
- La percepción del dolor está mediada por diferentes receptores que se encuentran a nivel de membrana de las neuronas nociceptivas.
- Estos receptores están especializados por estímulos o ligandos:



- Existen mecanismos de regulación de la expresión de estos receptores y de su respuesta a los estímulos.

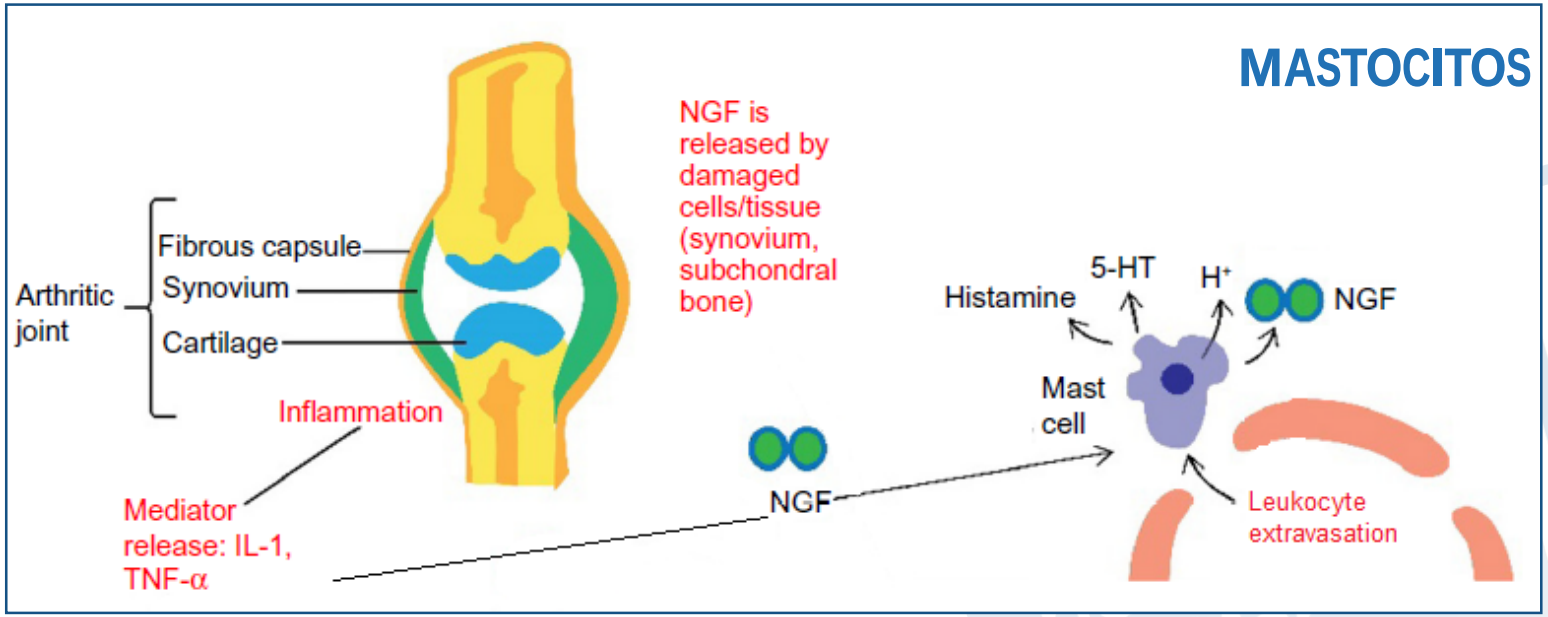
Fisiopatología

- Nerve Growth Factor (NGF): factor de crecimiento que pertenece a la familia de las neurotrofinas.
- Descubierto en la década de los 50 como factor que promueve el crecimiento y diferenciación de las neuronas.
- Las neurotrofinas actúan uniéndose a dos tipos de receptores celulares:
  - P75: receptor neurotrofina
  - Familia de receptores tirosina kinasa: son específicos de neurotrofina: NGF, trkA; BDNF,trkB; NT-3, trkC; and NT-4/5, trkB.

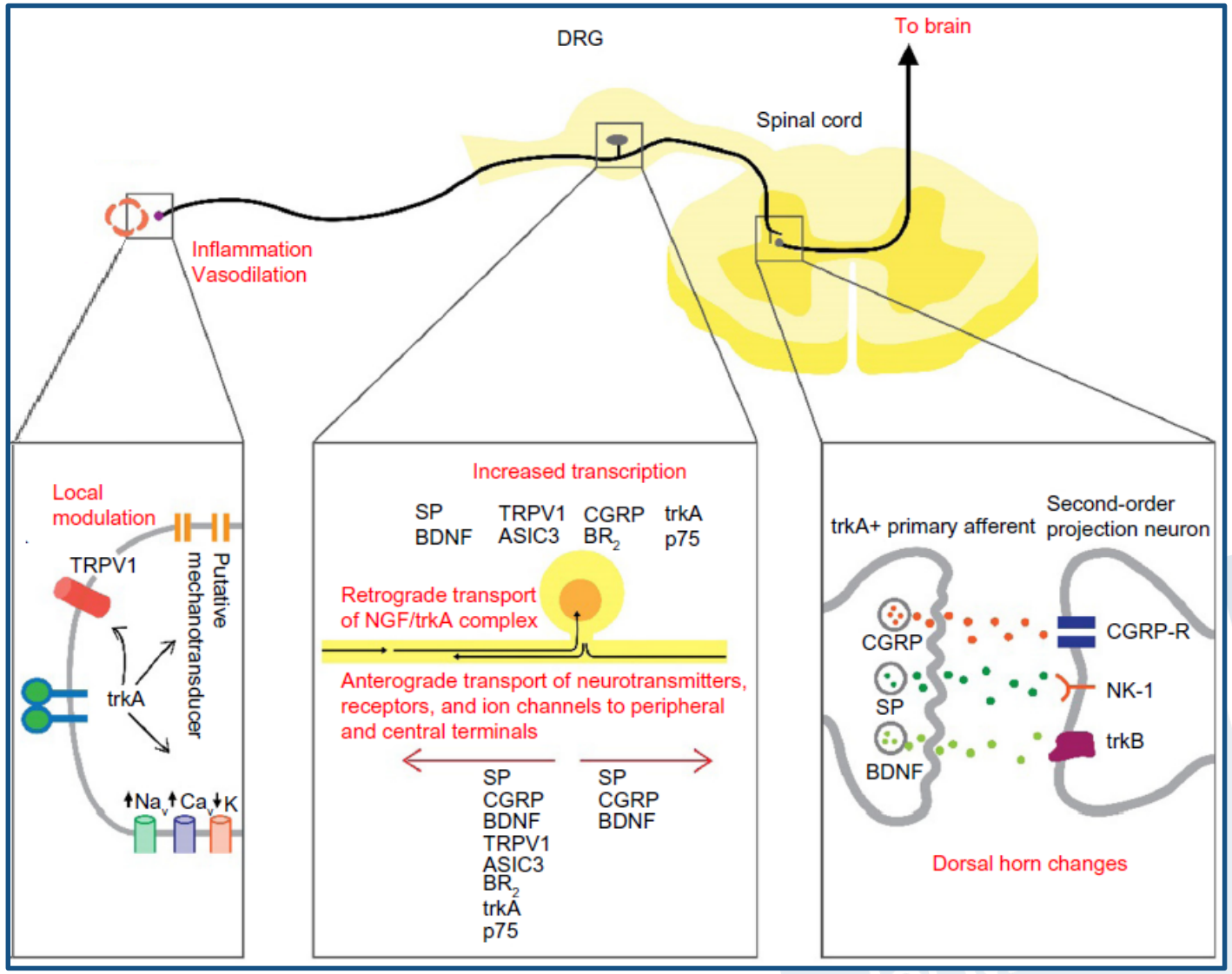


Chao, M. V. (2003). Neurotrophins and their receptors: A convergence point for many signalling pathways. Nature Reviews Neuroscience, 4(4), 299–309. doi:10.1038/nrn1078

- RoI NGF- trkA:
  - Embriogénesis: promover el crecimiento neuronal y la supervivencia.
  - Post natal: regular la sensibilidad del SNP a los estímulos nocivos
- NGF : producido por tejidos periféricos tras un estímulo nocivo, como resultado a la producción de citoquinas (TNF-α, IL-1β…)
- trkA: receptor en diferentes tipos celulares- múltiples efectos moduladores, principalmente en: axones aferentes y mastocitos.



Chang DS et al (2016) Anti-nerve growth factor in pain management: current evidence. J Pain Res. 2016 Jun 8;9:373-8

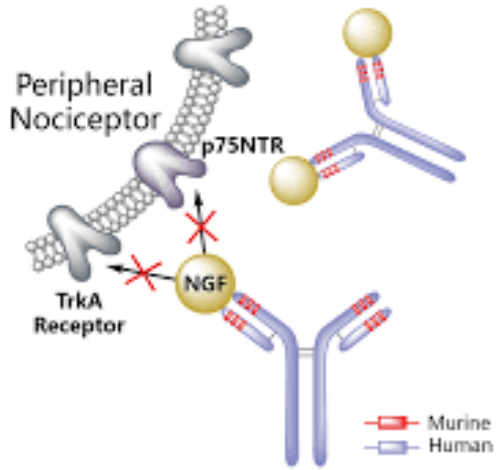


Chang DS et al (2016) Anti-nerve growth factor in pain management: current evidence. J Pain Res. 2016 Jun 8;9:373-8

- Desarrollado de varios enfoques contra la vía del NGF y su efecto en el inicio y el mantenimiento del dolor.
- Síntesis de Anticuerpos anti-NGF: se unen con alta especificidad a NGF inhibiendo su unión a trkA y p75.

TANEZUMAB

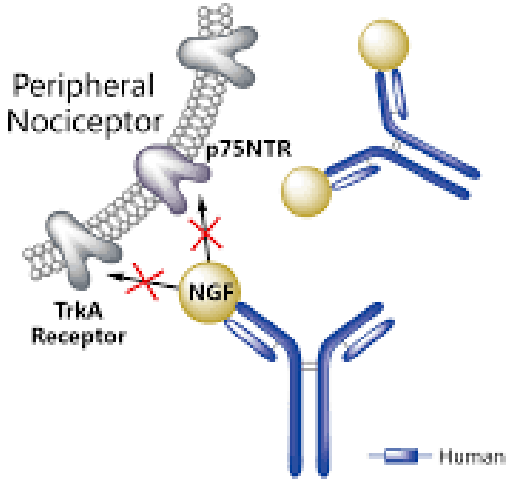
Anticuerpo monoclonal IgG2 humanizado (Fv murina, Fc humana



Pfizer y Eli Lilly

FASINUMAB

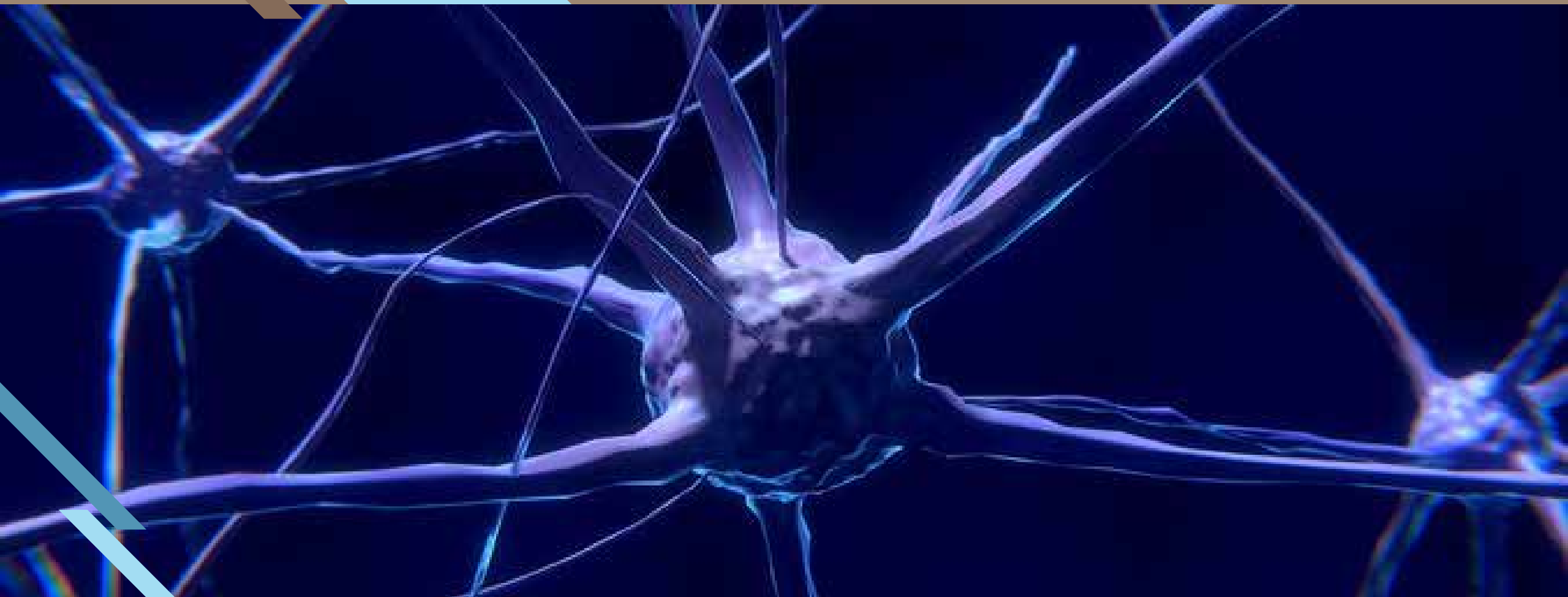
Anticuerpo recombinante monoclonal IgG4 humano



Regeneron Pharmaceuticals y Teva Pharmaceutical Industries Ltd. (NYSE y TASE: TEVA)

Anti NGF

Servei de Reumatologia
Hospital del **MAR**



Ensayos Clínicos Tanezumab

Tanezumab Reduces Osteoarthritic Knee Pain: Results of a Randomized, Double-Blind, Placebo-Controlled Phase III Trial

Mark T. Brown,* Frederick T. Murphy,[†,‡] D
Michael D. Smith,* and Christine R. West

Tanezumab Reduces Osteoarthritic Hip Pain

ind, Placebo-Controlled Phase III Trial

,[2] David M. Radin,[3] Isabelle Davignon,[1]
and Christine R. West[1]

Tanezumab for the Treatment of Pain from Osteoarthritis of the Knee

Nancy E. Lane, M
Masoud Mokh

Efficacy and safety of tanezumab versus naproxen in the treatment of chronic low back pain

Alan J. Kivitz [a,*], Joseph S. Gimbel [b], Candace Bramson [c], Mary Anne Nemeth [c], David S. Keller [c],

Efficacy and Safety of Subcutaneous Tanezumab for the Treatment of Osteoarthritis of the Hip or Knee

Thomas J. Schnitzer[1], Richard Easton[2], Shirley Pang[3], Dennis Levinson[4], Glenn Pixton[5], Lars Viktrup[6], Isabelle Davignon[7], Mark T. Brown[7], Kenneth M. Verburg[7] and Christine R. West[7], [1]Northwestern University, Chicago, IL, [2]Michigan Orthopaedic & Spine Surgeons, Rochester Hills, MI, [3]St. Jude Medical Center, Fullerton, CA, [4]Chicago Clinical Research Institute, Chicago, IL, [5]Pfizer, Inc., Morrisville, NC, [6]Eli Lilly and Company, Indianapolis, IN, [7]Pfizer, Inc., Groton, CT

Diseño del Estudio

Tanezumab Reduces Osteoarthritic Knee Pain: Results of a Randomized, Double-Blind, Placebo-Controlled Phase III Trial

Mark T. Brown,* Frederick T. Murphy,[†,‡] David M. Radin,[§] Isabelle Davignon,* Michael D. Smith,* and Christine R. West*

*Pfizer Inc, Groton, Connecticut.
[†]Altoona Center for Clinical Research, Duncansville, Pennsylvania.
[‡]University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.
[§]Stamford Therapeutics Consortium, Stamford, Connecticut.

Tanezumab Reduces Osteoarthritic Hip Pain

Results of a Randomized, Double-Blind, Placebo-Controlled Phase III Trial

Mark T. Brown,[1] Frederick T. Murphy,[2] David M. Radin,[3] Isabelle Davignon,[1] Michael D. Smith,[1] and Christine R. West[1]

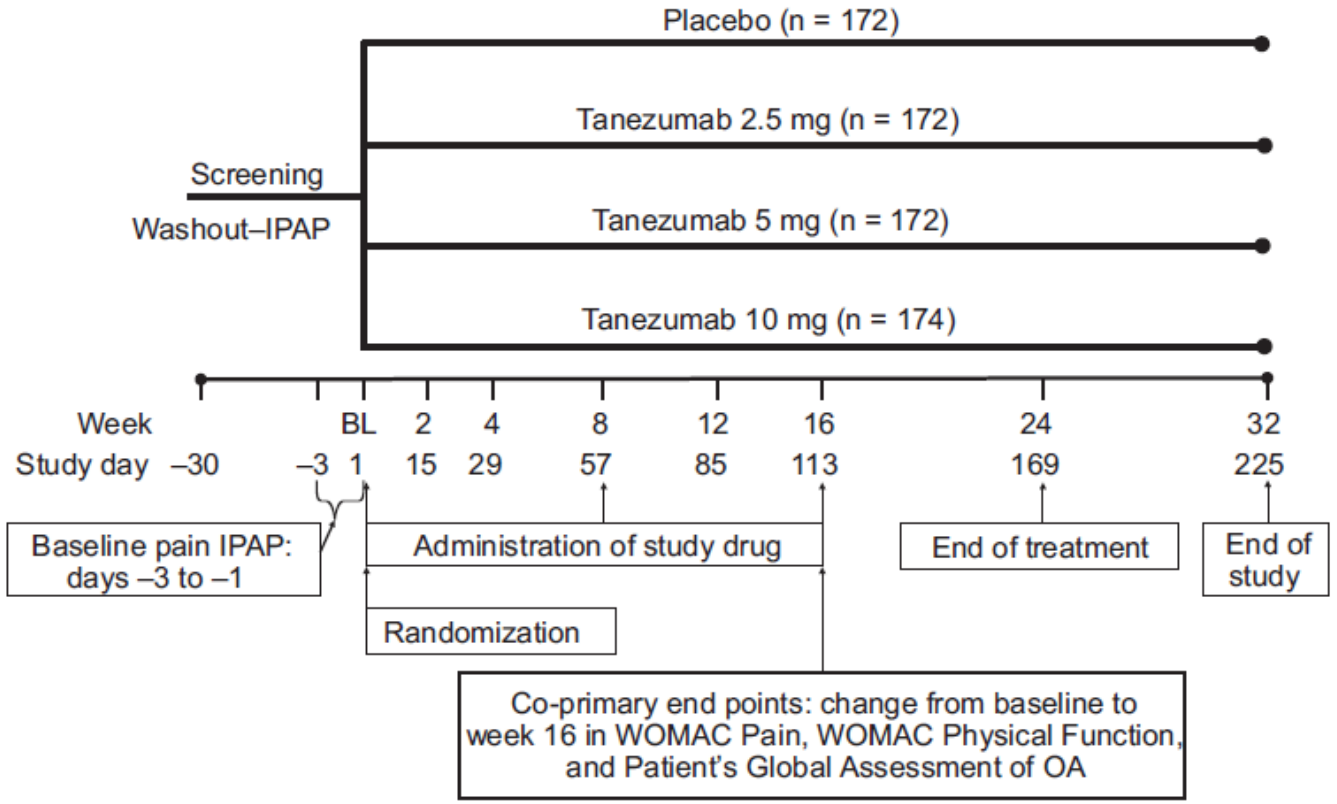
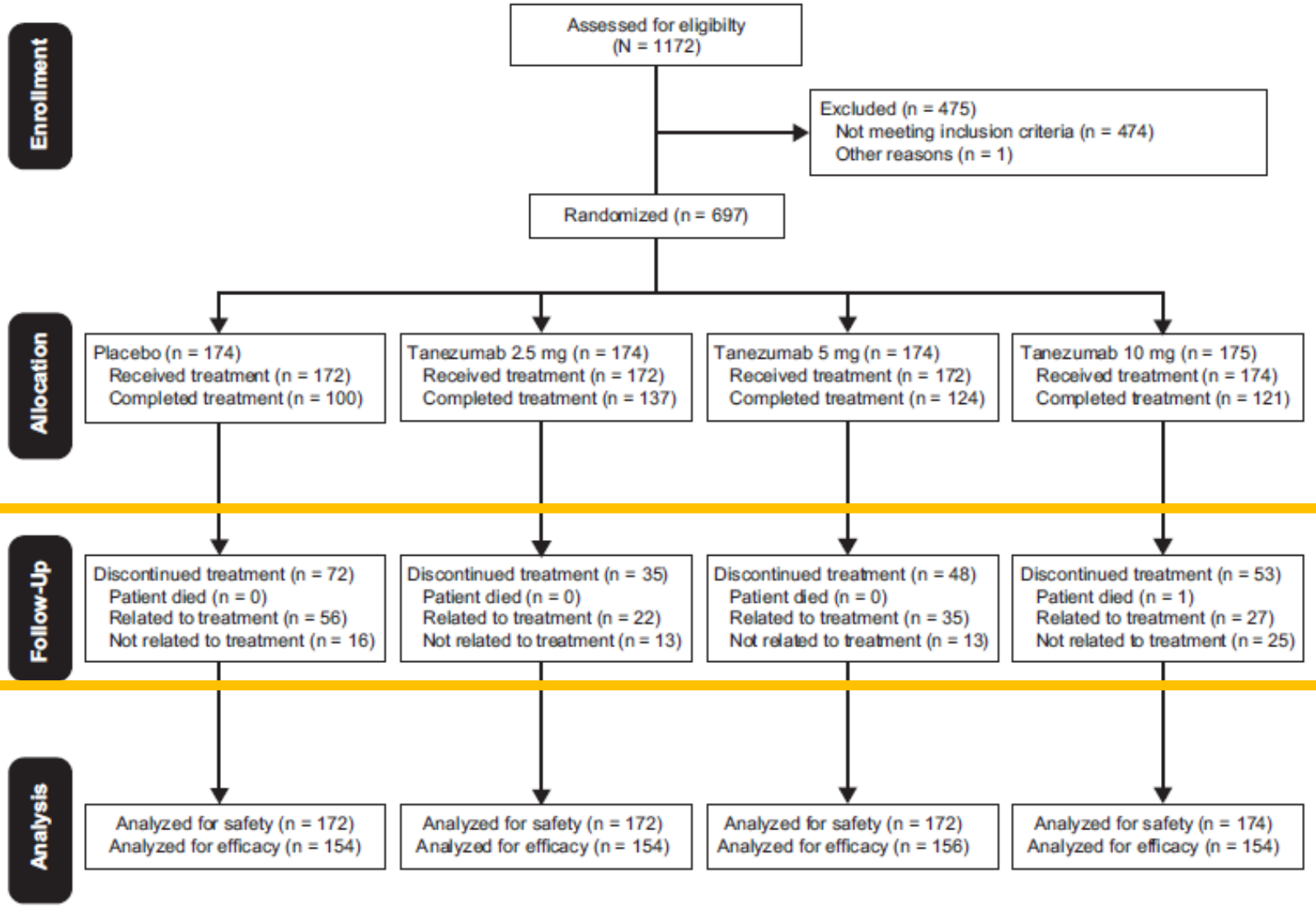


Figure 1. Study design. Abbreviations: IPAP, initial pain assessment period; BL, baseline.

Brown et al. Tanezumab Reduces Osteoarthritic Knee Pain: Results of Randomized, Double-Blind, Placebo-Controlled Phase III trial. J Pain. 2012 Aug;13(8):790-8
Brown et al. Tanezumab Reduces Osteoarthritic Hip Pain.: **results of a randomized, double-blind, placebo-controlled phase III trial** Arthritis Rheum. 2013 Jul;65(7):1795-803.

Diagrama de flujo



RESULTADOS

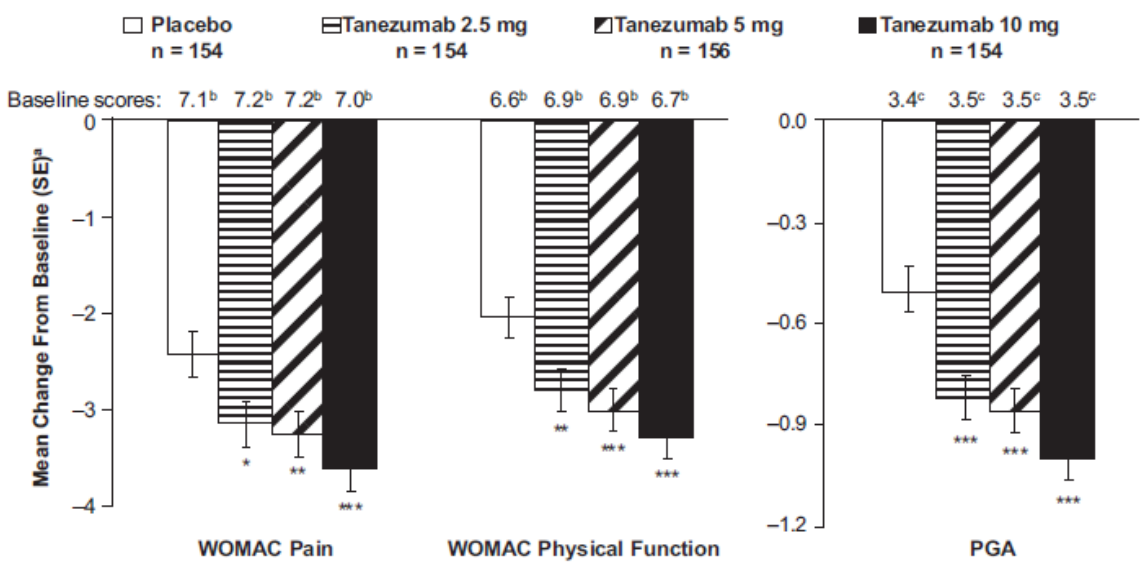
Table 1. Baseline characteristics of the patients with hip osteoarthritis in the intent-to-treat population, by treatment group

	Placebo (n = 155)	Tanezumab 2.5 mg (n = 155)	Tanezumab 5 mg (n = 154)	Tanezumab 10 mg (n = 157)
Sex, no. (%) male/female	52 (33.5)/103 (66.5)	54 (34.8)/101 (65.2)	62 (40.3)/92 (59.7)	69 (43.9)/88 (56.1)
Age, mean (range) years	61.9 (31–88)	62.4 (26–88)	61.8 (21–88)	63.3 (35–92)
Kellgren/Lawrence grade, no. (%)				
Grade 1	0	0	1 (0.6)	0
Grade 2	73 (47.1)	71 (45.8)	72 (46.8)	67 (42.7)
Grade 3				58 (36.9)
Grade 4				32 (20.4)
Duration since diagn (range) years				5.6 (0–59)
Candidates for invasi interventions, no.				80 (51.0)

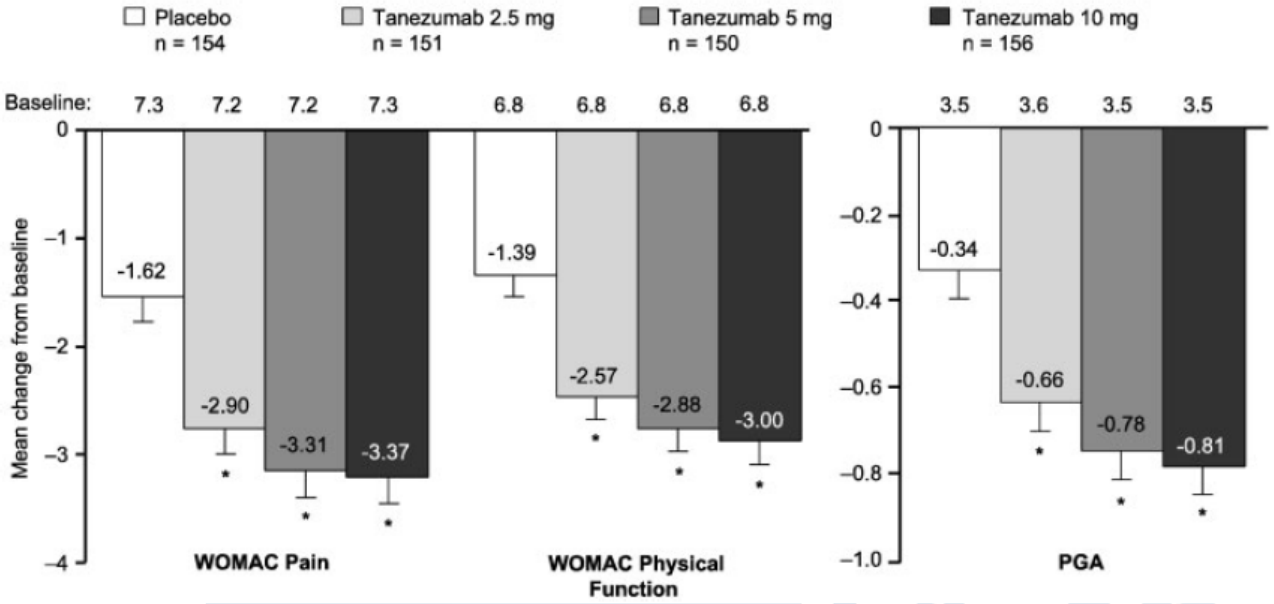
Knee

Kellgren-Lawrence grade, n (%)				
Grade 2	68 (39.5)	64 (37.2)	64 (37.2)	71 (40.8)
Grade 3	82 (47.7)	74 (43.0)	89 (51.7)	77 (44.3)
Grade 4	22 (12.8)	31 (18.0)	18 (10.5)	26 (14.9)
Missing data	0	3 (1.7)	1 (.6)	0
Candidates for invasive interventions*, n (%)				
Candidates	91 (52.9)	80 (46.5)	78 (45.3)	83 (47.7)

Endpoints Primarios



Rodilla



Cadera

Tanezumab Reduces Osteoarthritic Knee/Hip Pain (Brown et al.)

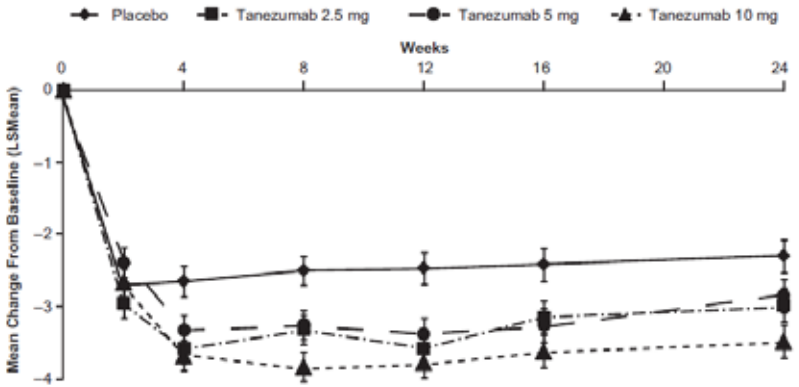


Figure 5. Summary of WOMAC pain subscale, change from baseline to week 24 (modified intent-to-treat population). Baseline observation carried forward imputation for missing data. Abbreviations: LS, least squares; SE, standard error.

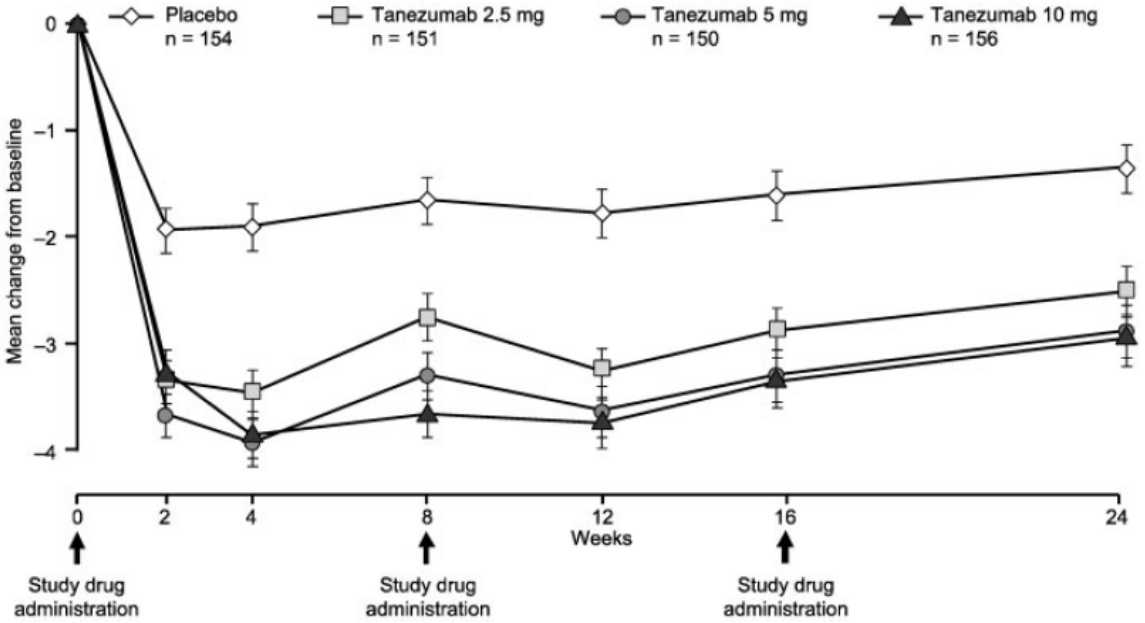


Figure 3. Change from baseline to week 24 in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale in patients with hip OA. Data are from the modified intent-to-treat population, as described in Patients and Methods, with baseline observation carried forward imputation used for patients with missing data. The WOMAC Pain subscale was assessed using a 0–10-point numerical rating scale. Values are the least squares mean ± SEM. $P < 0.001$ versus placebo for all tanezumab groups at all time points starting with week 2.

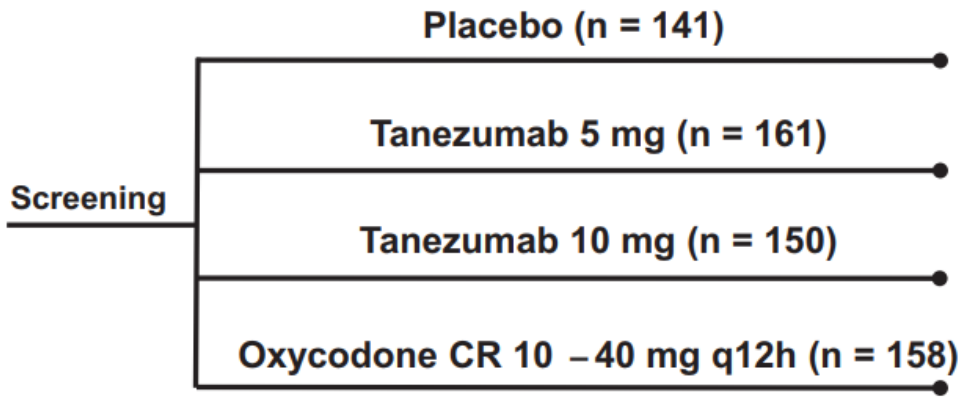
Tanezumab- Oxycodone

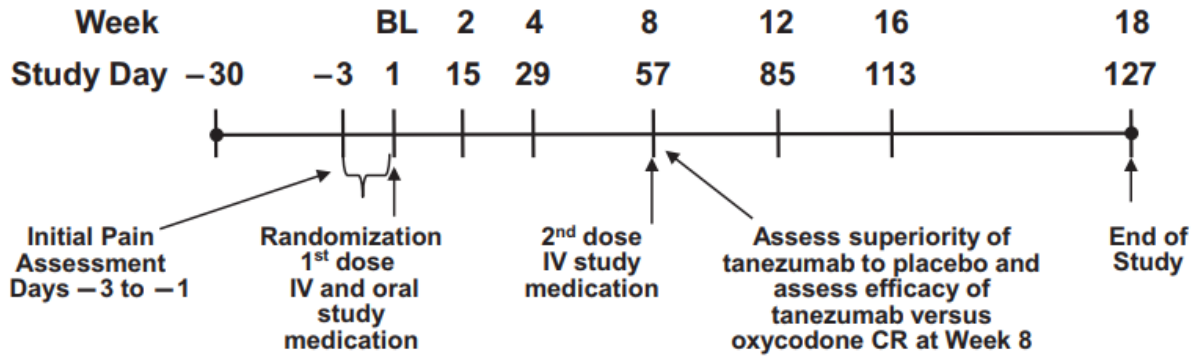
Pain. 2013 Sep;154(9):1603-12. doi: 10.1016/j.pain.2013.04.035. Epub 2013 Apr 22.

A phase III placebo- and oxycodone-controlled study of tanezumab in adults with osteoarthritis pain of the hip or knee.

Spierings EL[1], Fidelholtz J, Wolfram G, Smith MD, Brown MT, West CR.

Doble-blind, randomized, placebo-controlled, multicenter, parallel-group, phase III study
n= 610 patients





Spiering et al. A phase III placebo- and oxycodone-controlled study of tanezumab in adults with osteoarthritis pain of the hip or knee. Pain. 2014 Nov;155(11):2432-3.

Resultados

	IIT				mITT			
	Placebo	Tanezumab 5 mg	Tanezumab 10 mg	Oxycodone CR 10 to 40 mg every 12 h	Placebo	Tanezumab 5 mg	Tanezumab 10 mg	Oxycodone CR 10 to 40 mg every 12 h
WOMAC Pain subscale								
n	141	161	150	158	137	153	149	156
Baseline scores, mean (SD)	7.75 (1.21)	7.85 (1.27)	7.63 (1.30)	7.85 (1.27)	7.75 (1.20)	7.87 (1.26)	7.64 (1.31)	7.86 (1.27)
LSM change from baseline at week 8 (SE)	−2.62 (0.24)	−3.58 (0.22)	−3.58 (0.23)	−2.59 (0.22)	−2.28 (0.26)	−3.14 (0.24)	−2.81 (0.24)	−2.17 (0.24)
P value versus placebo		<.001	<.001					.700
P value versus oxycodone CR 10 to 40 mg every 12 h						<.001	.018	
WOMAC Physical Function subscale								
n	140	161	150	158	136	153	149	156
Baseline scores, mean (SD)	7.19 (1.50)	7.30 (1.58)	7.04 (1.54)	7.25 (1.53)	7.17 (1.51)	7.32 (1.59)	7.05 (1.54)	7.26 (1.53)
LSM change from baseline at week 8 (SE)	−1.91 (0.23)	−3.05 (0.20)	−3.06 (0.21)	−2.05 (0.21)	−1.67 (0.24)	−2.78 (0.22)	−2.52 (0.23)	−1.71 (0.22)
P value versus placebo		<.001	<.001					.898
P value versus oxycodone CR 10 to 40 mg every12 h						<.001	.002	
WOMAC Stiffness subscale								
n	141	161	150	158	137	153	149	156
Baseline scores, mean (SD)	7.22 (1.67)	7.30 (1.92)	7.15 (1.82)	7.39 (1.72)	7.22 (1.69)	7.29 (1.93)	7.16 (1.82)	7.39 (1.72)
LSM change from baseline at week 8 (SE)	−1.85 (0.23)	−3.01 (0.21)	−3.27 (0.22)	−2.07 (0.21)	−1.54 (0.25)	−2.77 (0.23)	−2.58 (0.24)	−1.69 (0.23)
P value versus placebo		<.001	<.001					.568
P value versus oxycodone CR 10 to 40 mg every 12 h						<.001	.001	
Patient's Global Assessment of OA								
n	141	161	150	158	137	153	149	156
Baseline scores, mean (SD)	3.60 (0.68)	3.58 (0.65)	3.57 (0.68)	3.59 (0.62)	3.59 (0.68)	3.59 (0.65)	3.56 (0.68)	3.59 (0.62)
LSM change from baseline at week 8 (SE)	−0.52 (0.08)	−0.90 (0.07)	−1.00 (0.08)	−0.55 (0.07)	−0.51 (0.08)	−0.90 (0.07)	−0.79 (0.08)	−0.50 (0.07)
P value versus placebo		<.001	<.001					.876
P value versus oxycodone CR 10 to 40 mg every 12 h						<.001	<.001	

Spiering et al. A phase III placebo- and oxycodone-controlled study of tanezumab in adults with osteoarthritis pain of the hip or knee. Pain. 2014 Nov;155(11):2432-3.

Osteoarthritis and Cartilage

OARSI

Review

A systematic review of the efficacy and general safety of antibodies to NGF in the treatment of OA of the hip or knee

T.J. Schnitzer*, J.A. Marks

Northwestern University Feinberg School of Medicine, 303 E. Chicago Avenue, Chicago, IL, 60611, USA

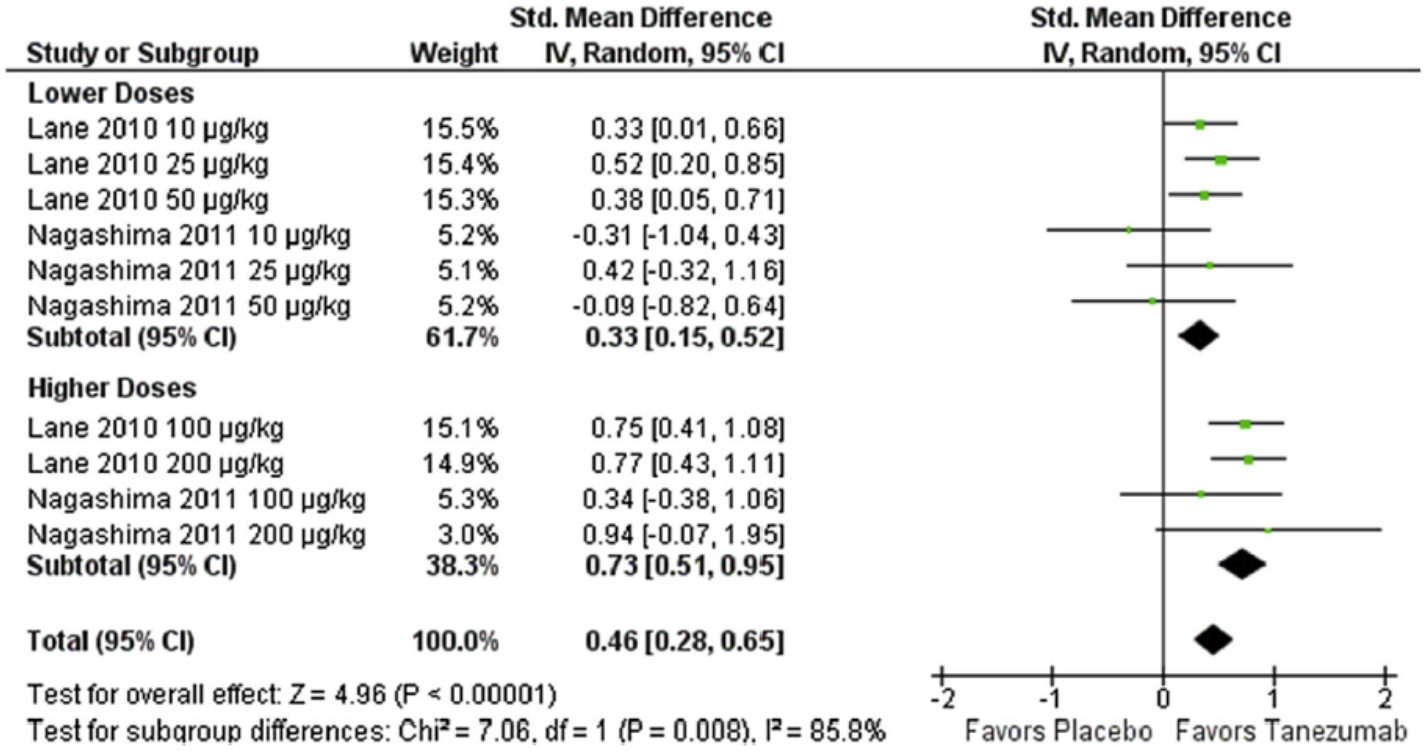


Fig. 1. Phase II efficacy data; standard mean change [95% CI] in WOMAC pain compared to baseline by dosing group.

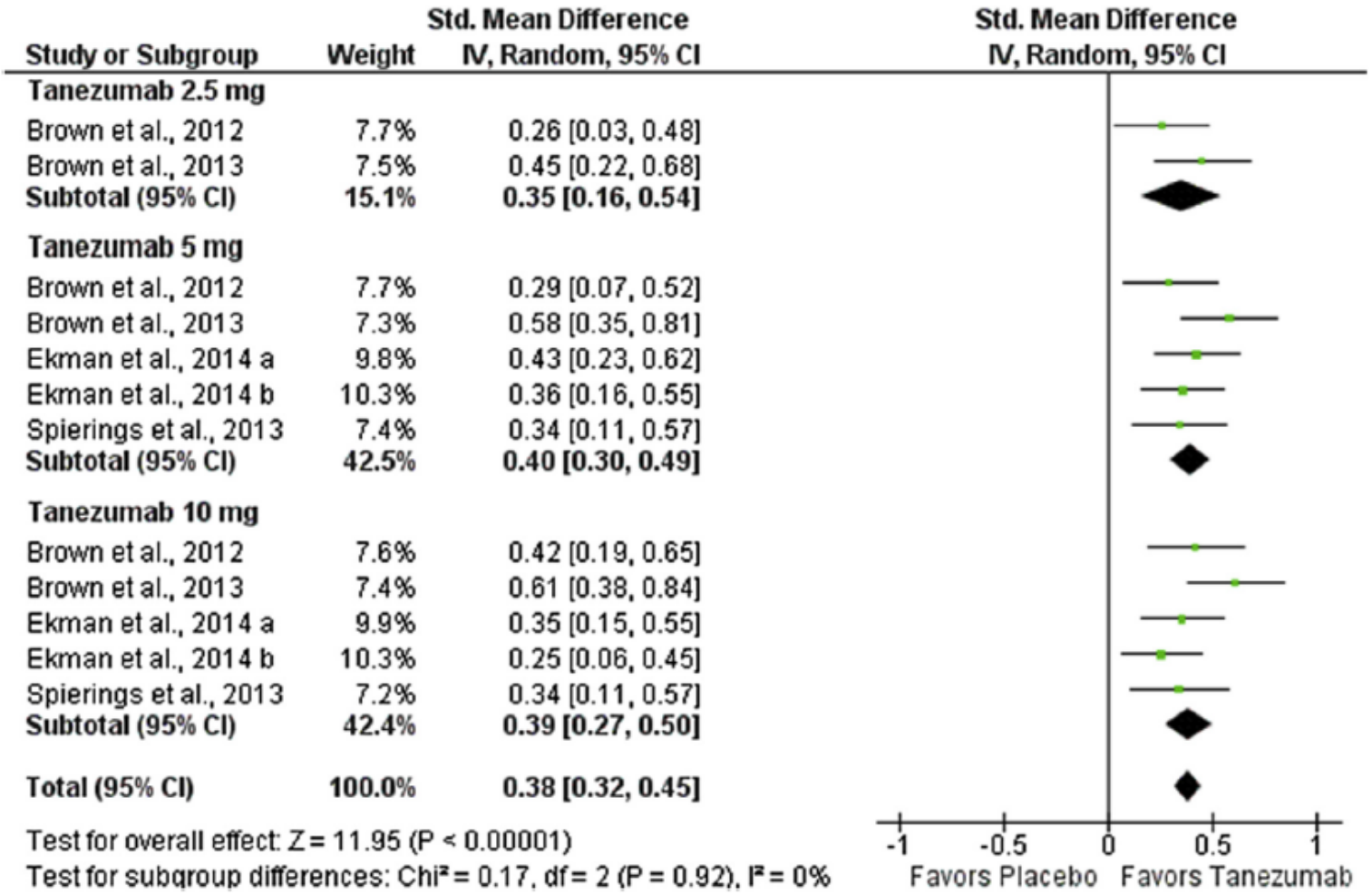


Fig. 2. Phase III efficacy data; standard mean change [95% CI] in WOMAC pain compared to baseline by dosing group.

Tanezumab: Diseño del Estudio

ABSTRACT NUMBER: L20

Efficacy and Safety of Subcutaneous Tanezumab for the Treatment of Osteoarthritis of the Hip or Knee

Thomas J. Schnitzer[1], Richard Easton[2], Shirley Pang[3], Dennis Levinson[4], Glenn Pixton[5], Lars Viktrup[6], Isabelle Davignon[7], Mark T. Brown[7], Kenneth M. Verburg[7] and Christine R. West[7], [1]Northwestern University, Chicago, IL, [2]Michigan Orthopaedic & Spine Surgeons, Rochester Hills, MI, [3]St. Jude Medical Center, Fullerton, CA, [4]Chicago Clinical Research Institute, Chicago, IL, [5]Pfizer, Inc., Morrisville, NC, [6]Eli Lilly and Company, Indianapolis, IN, [7]Pfizer, Inc., Groton, CT

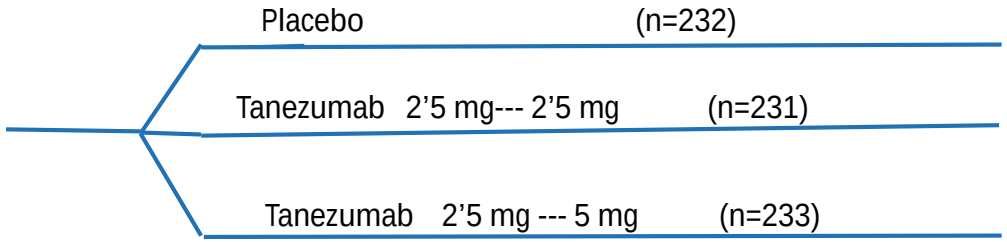
Meeting: 2018 ACR/ARHP Annual Meeting

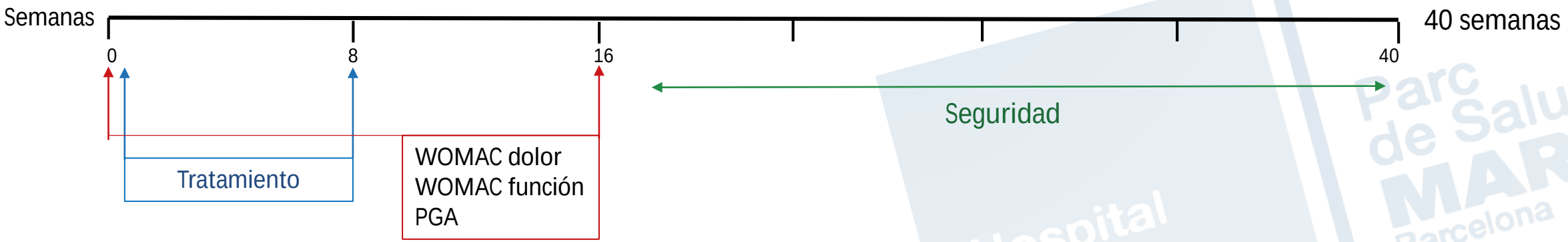
Date of first publication: October 4, 2018

Doble-blind, randomized, placebo-controlled,

multicenter, parallel-group

n= 699 patients





Resultados: Eficacia

	placebo	tanezumab 2.5 mg	tanezumab 2.5/5 mg
	N = 232	N = 231	N = 233
WOMAC Pain[a]			
Mean (Range) Baseline Pain Score	7.30 (4.2, 10.0)	7.08 (4.8, 10.0)	7.33 (5.0, 10.0)
LS Mean (SE) Change from Baseline	-2.64 (0.23)	-3.23 (0.23)	-3.37 (0.22)
Diff of LS Means (SE)		-0.60 (0.24)	-0.73 (0.24)
p-value		0.0129	0.0023
WOMAC Physical Function[b]			
Mean (Range) Baseline Physical Function Score	7.38 (4.4, 10.0)	7.18 (5.1, 9.9)	7.39 (3.2, 9.9)
LS Mean (SE) Change from Baseline	-2.56 (0.22)	-3.22 (0.22)	-3.45 (0.22)
Diff of LS Means (SE)		-0.66 (0.24)	-0.89 (0.24)
p-value		0.0065	0.0002
PGA-OA[c]			
Mean (Range) Baseline Score	3.46 (3, 5)	3.42 (2, 5)	3.53 (3, 5)
LS Mean (SE) Change from Baseline	-0.65 (0.08)	-0.87 (0.08)	-0.90 (0.08)
Diff of LS Means (SE)		-0.22 (0.09)	-0.25 (0.09)
p-value		0.0109	0.0038

Resultados: Seguridad

	placebo	tanezumab 2.5 mg	tanezumab 2.5/5 mg
	N = 232	N = 231	N = 233
Adverse events			
Any adverse event, n (%)	115 (49.6)	128 (55.4)	109 (46.8)
Any treatment-related adverse event, n (%)	24 (10.3)	29 (12.6)	22 (9.4)
Any treatment discontinuation due to adverse events, n (%)[a]	2 (0.9)	0	1 (0.4)
Any study withdrawal due to adverse events, n (%)	2 (0.9)	1 (0.4)	2 (0.9)
Any serious adverse event, n (%)	4 (1.7)	4 (1.7)	4 (1.7)
Adverse event, n (%)			
Arthralgia	29 (12.5)	19 (8.2)	22 (9.4)
Nasopharyngitis	8 (3.4)	12 (5.2)	11 (4.7)
Musculoskeletal pain	8 (3.4)	7 (3.0)	2 (0.9)
Back pain	7 (3.0)	10 (4.3)	6 (2.6)
Headache	7 (3.0)	6 (2.6)	7 (3.0)
Fall	6 (2.6)	11 (4.8)	5 (2.1)
Upper respiratory tract infection	6 (2.6)	7 (3.0)	3 (1.3)
Joint swelling	4 (1.7)	8 (3.5)	4 (1.7)
Pain in extremity	2 (0.9)	4 (1.7)	7 (3.0)
Paresthesia	1 (0.4)	8 (3.5)	3 (1.3)

Efficacy and Safety of Subcutaneous Tanezumab for the Treatment of Osteoarthritis of the Hip ot Knee. (J Schintzer et al)

Fasinumab: Diseño del Estudio

Fasinumab (REGN475), an antibody against nerve growth factor for the treatment of pain: Results from a double-blind, placebo-controlled exploratory study in osteoarthritis of the knee

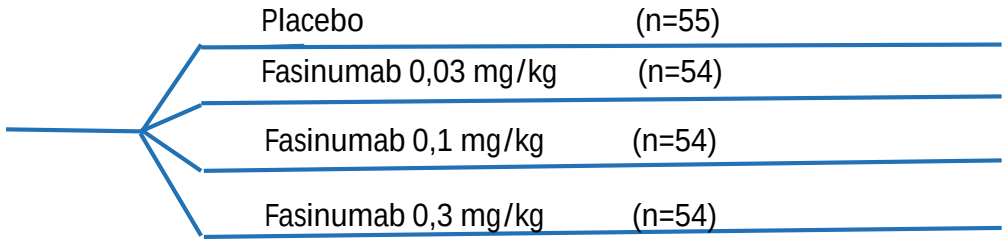
Paul J. Tiseo [a,*], Alan J. Kivitz [b], John E. Ervin [c], Haobo Ren [a], Scott J. Mellis [a]

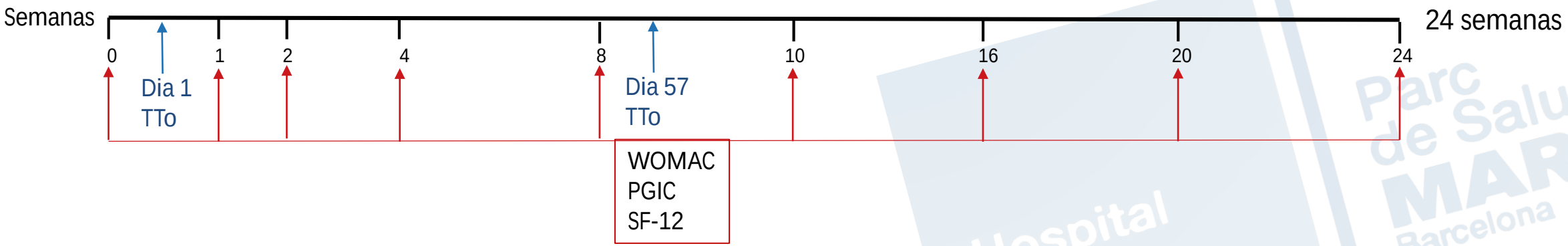
[a] Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA
[b] Altoona Center for Clinical Research, Duncansville, PA, USA
[c] The Center for Pharmaceutical Research, Kansas City, MO, USA

Doble-blind, randomized, placebo-controlled,

exploratory dose-ranging study

n= 217 patients





Tiseo et al. Fasinumab (REGN475), an antibody against verve growth factor for the treatment of pain: Results from a double-blind, placebo-controlled exploratory study in osteoarthritis of the knee. Pain. 2014 Jul;155(7):1245-52.

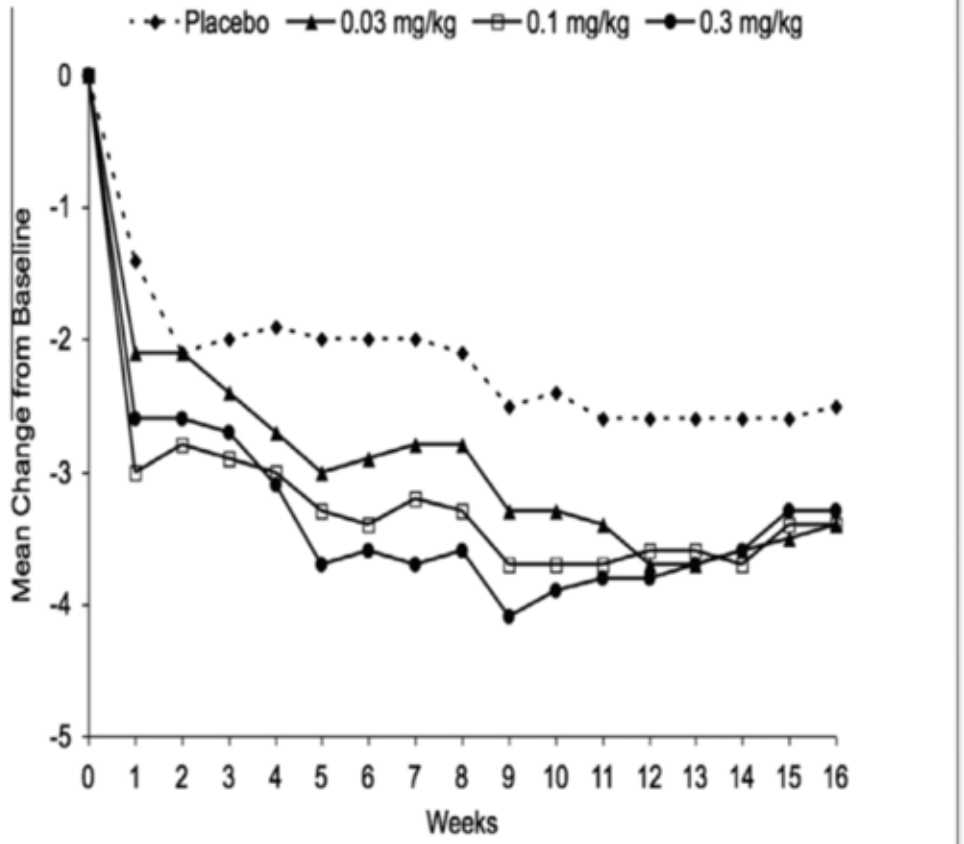


Fig. 2. Mean change from baseline to week 16 for walking knee pain.

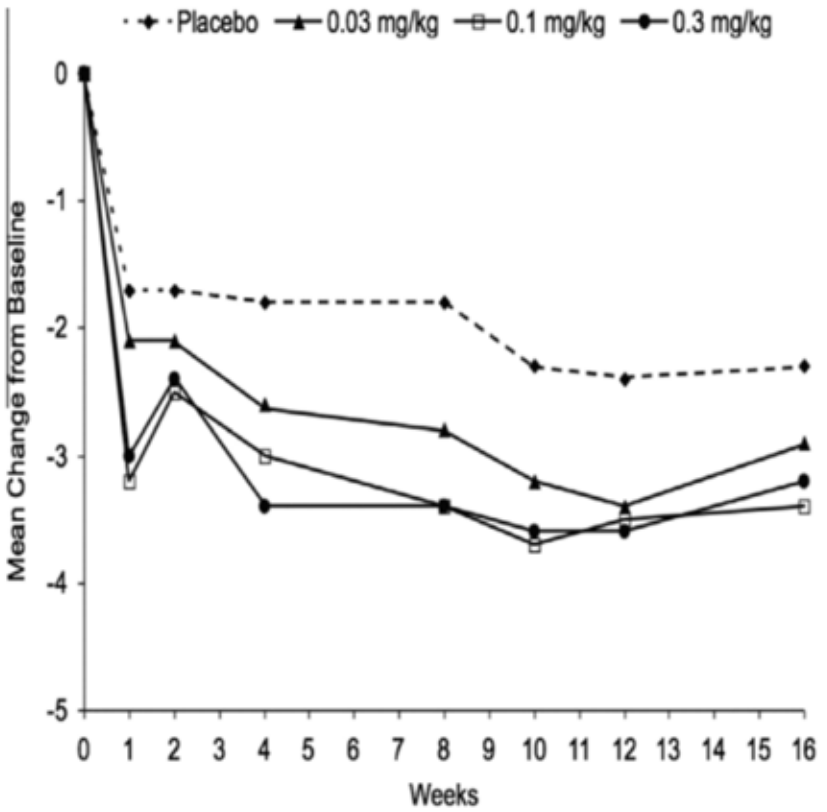


Fig. 3. Change from baseline to week 16 for Western Ontario and McMaster Osteoarthritis total score.

Resultados

Table 4
Change from baseline to week 16 in walking knee pain numerical rating scale scores—observed data using MMRM full analysis set (FAS).

	Placebo (N = 55)	Fasinumab		
		0.03 mg/kg (N = 53)	0.1 mg/kg (N = 53)	0.3 mg/kg (N = 54)
Mean (SD) baselinewalking knee pain	6.4 (1.69)	6.6 (1.65)	6.5 (1.53)	6.6 (1.47)
Week 8				
Mean (SD) change from baseline to week 8	−2.1(2.08)	−2.8(2.29)	−3.3(2.61)	−3.6(2.48)
Difference vs placebo least-squares mean (SE)		−0.7(0.43)	−1.2(0.42)	−1.3(0.43)
P value via MMRM		.0981	.0053	.0035
Week 16				
Mean (SD) change from baseline to week 16	−2.5(2.15)	−3.4(2.24)	−3.4(2.58)	−3.3(2.55)
Difference vs placebo least-squares mean (SE)		−1.1(0.46)	−1.0(0.46)	−0.9(0.47)
P value via MMRM		.0229	.0267	.0631

MMRM = mixed-effects model–repeated measures.

Table 5
Western Ontario and McMaster Osteoarthritis numerical rating scale pain subscale—change from baseline to week 16, observed data using MMRM (full analysis set).

	Placebo (N = 55)	Fasinumab		
		0.03 mg/kg (N = 53)	0.1 mg/kg (N = 53)	0.3 mg/kg (N = 54)
Mean (SD) baseline pain score	5.9 (1.79)	5.7 (1.77)	6.1 (1.75)	6.4 (1.97)
Week 8				
Mean (SD) change from baseline to week 8	−1.9 (1.74)	−2.6 (2.01)	−3.4 (2.54)	−3.5 (2.42)
Difference vs placebo least-squares mean (SE)		−0.9 (0.39)	−1.4 (0.39)	−1.3 (0.39)
P value via MMRM		.0228	.0003	.0010
Week 16				
Mean (SD) change from baseline to week 16	−2.4 (2.18)	−2.7 (1.89)	−3.4 (2.53)	−3.2 (2.24)
Difference vs placebo least-squares mean (SE)		−0.6 (0.42)	−1.1 (0.42)	−0.8 (0.42)
P value via MMRM		.1486	.0090	.0488

MMRM = mixed-effects model–repeated measures.

Fasinumab: Diseño del Estudio

ABSTRACT NUMBER: 295

Efficacy and Safety of Fasinumab for Osteoarthritic Pain in Patients with Moderate to Severe Osteoarthritis of the Knees or Hips

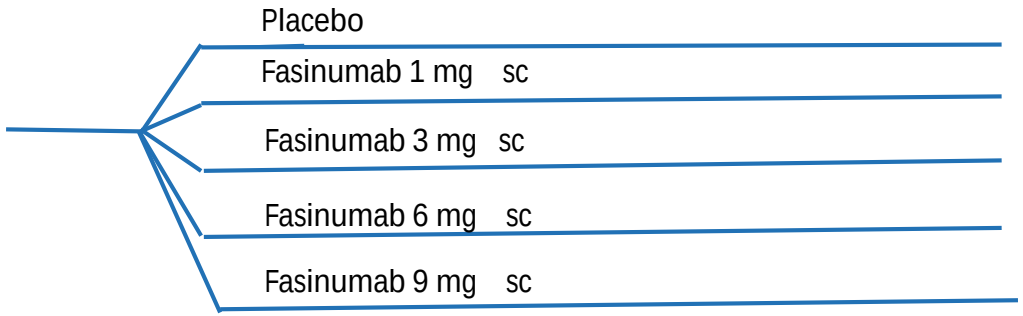
Jennifer Maloney[1], Alan Kivitz[2], Thomas J. Schnitzer[3], Paula Dakin[1], Catherine Stehman-Breen[1] and Greg Geba[1], [1]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [2]Altoona Center for Clinical Research, Duncansville, PA, [3]Northwestern University, Chicago, IL

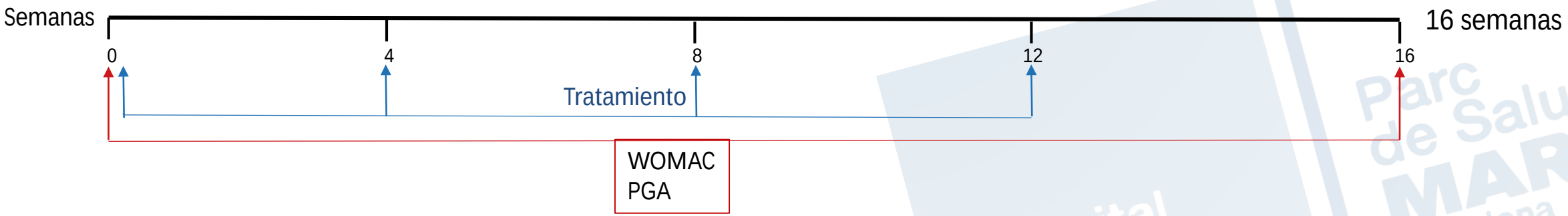
Meeting: 2016 ACR/ARHP Annual Meeting

Date of first publication: September 28, 2016

Doble-blind, randomized, placebo-controlled

n= 490 patients





- Eficacia y seguridad

Tratamiento	Cambios WOMAC dolor respecto al inicio	Fractura por insuficiencia	Artrosis rápidamente progresiva
Placebo	-2’25	1	0
Fasinumab 1 mg	-3’35 (p≤0’05)	0	0
Fasinumab 3 mg	-3’33 (p≤0’05)	2	1
Fasinumab 6 mg	-3’03 (p≤0’05)	0	1
Fasinumab 9 mg	-3’5 (p≤0’05)	4	1

Efectos Adversos

Servei de Reumatologia
Hospital del **MAR**

Table IV
Comparison of withdrawals due to AEs in tanezumab, tanezumab + NSAID, placebo and placebo + NSAID groups

Study, year	All anti-NGF groups			Placebo			All tanezumab + Active comparator				Placebo + Active comparator		
	Withdrawals	Subjects	%	Withdrawals	Subjects	%	Withdrawals	Subjects	%		Withdrawals	Subjects	%
Balanescu *et al.*, 2013							28	452	6.2%	†	6	152	3.9%
Brown *et al.*, 2012	23	516	4.5%	3	172	1.7%							
Brown *et al.*, 2013	20	466	4.3%	6	155	3.9%							
Ekman *et al.*, 2011 a	29	414	7.0%	7	208	3.4%				*	13	206	6.3%
Ekman *et al.*, 2011 b	18	420	4.3%	10	209	4.8%				*	16	211	7.6%
Lane *et al.*, 2010	22	370	5.9%	0	74	0.0%							
Mayorga *et al.*, 2014	6	98	6.1%	2	48	4.2%				‡	14	50	28.0%
Nagashima *et al.*, 2011	0	67	0.0%	0	16	0.0%							
Sanga *et al.*, 2013	10	388	2.6%	1	78	1.3%							
Schnitzer *et al.*, 2014	151	1083	13.9%				176	1078	16.3%	*	49	539	9.1%
Spierings *et al.*, 2013	6	311	1.9%	2	141	1.4%				‡	16	158	10.1%
Tiseo *et al.*, 2014	9	160	5.6%	2	55	3.6%							
Total	294	4371	6.8%	33	1156	2.9%	204	1530	13.3%		114	1316	8.7%

* NSAID.
† DSR.
‡ Oxycodone.

ALTERACIONES NEUROLÓGICAS PERIFÉRICAS

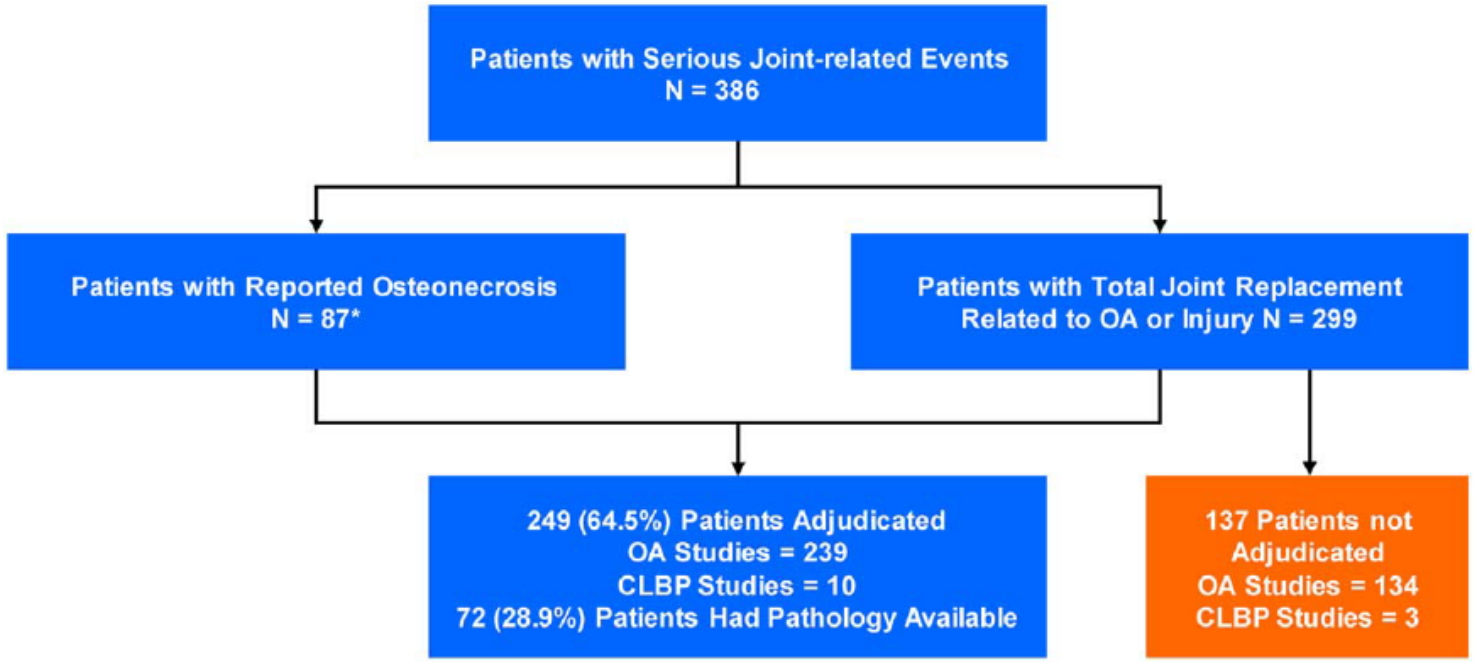
Brown et al.

	Placebo (n = 155)	Tanezumab 2.5 mg (n = 155)	Tanezumab 5 mg (n = 154)	Tanezumab 10 mg (n = 157)
AEs of abnormal peripheral sensation, no. (%)				
Paresthesia	6 (3.9)	8 (5.2)	4 (2.6)	8 (5.1)
Hypoesthesia	3 (1.9)	6 (3.9)	2 (1.3)	3 (1.9)
Burning sensation	0	1 (0.6)	1 (0.6)	3 (1.9)
Peripheral neuropathy	0	2 (1.3)	0	3 (1.9)
Dysesthesia	0	1 (0.6)	0	2 (1.3)
Decreased vibratory sense	0	0	0	2 (1.3)
Hyperesthesia	0	0	1 (0.6)	1 (0.6)
Facial hypoesthesia	0	1 (0.6)	0	0
Polyneuropathy	1 (0.6)	0	0	0

Ekman et al.

	Placebo, n = 208	Tanezumab 5 mg*, n = 206	Study 1015 Tanezumab 10 mg*, n = 208	Naproxen 500 mg BID, n = 206
AE of abnormal peripheral sensation‡				
Allodynia	0	0	5 (2.4)	0
Burning sensation	1 (0.5)	2 (1.0)	3 (1.4)	1 (0.5)
Decreased vibratory sense	1 (0.5)	2 (1.0)	2 (1.0)	1 (0.5)
Dysesthesia	1 (0.5)	0	2 (1.0)	0
Facial hypoesthesia	0	0	0	1 (0.5)
Hyperesthesia	1 (0.5)	1 (0.5)	2 (1.0)	0
Hypoesthesia	2 (1.0)	4 (1.9)	10 (4.8)	8 (3.9)
Neuralgia	0	1 (0.5)	0	0
Paresthesia	3 (1.4)	12 (5.8)	18 (8.7)	6 (2.9)
Peripheral neuropathy	0	1 (0.5)	1 (0.5)	0
Peripheral sensory neuropathy	0	0	0	0
Sensory disturbance	0	1 (0.5)	1 (0.5)	0

OSTEONECROSIS



* *50 patients (57.5%) underwent total joint replacement.*

Figure 1. Flow diagram of adjudicated events in the tanezumab clinical program. OA = osteoarthritis; CLBP = chronic low back pain. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/doi/10.1002/art.39492/abstract

OSTEONECROSIS

Table 2. Adjudication outcomes categorized by investigator report*

Outcome (category no.)†	Reported ON (n = 87)	Total joint replacement related to OA or joint injury/infection (n = 162)	Total (n = 249)
Primary ON (1)	2 (2.3)	0 (0.0)	2 (0.8)
Worsening OA (2)	51 (58.6)	149 (92.0)	200 (80.3)
Rapid progression, type 1 (2a–1)	3 (3.5)	8 (4.9)	11 (4.4)
Rapid progression, type 2 (2a–2)	31 (35.6)	26 (16.0)	57 (22.9)
Normal progression (2b)	14 (16.1)	105 (64.8)	119 (47.8)
Insufficient information to distinguish between rapid and normal progression (2c)	3 (3.4)	10 (6.2)	13 (5.2)
Other, with diagnosis specified (3)	21 (24.1)	8 (4.9)	29 (11.6)
Not enough information to distinguish primary ON from worsening OA or to specify another diagnosis (4)	8 (9.2)	3 (1.9)	11 (4.4)
Lack of consensus‡	5 (5.8)	2 (1.2)	7 (2.8)

* Values are the number (%). ON = osteonecrosis; OA = osteoarthritis.
† Category numbers correspond to those used in Patients and Methods.
‡ Fewer than 3 Adjudication Committee members agreed on the final assessment.

When Is Osteonecrosis Not Osteonecrosis? Adjudication of Reported Serious Adverse Joint Events in the Tanezumab Clinical Develpoment Program (Hochberg).

OSTEONECROSIS

Table 3. HRs for RPOA in phase III OA studies

	RPOA type 1, no. of events	RPOA type 2, no. of events	Treatment comparisons, HR (95% CI)*
Tanezumab 5 mg	3	11	4.10 (0.50–33.4)
Tanezumab 10 mg	4	18	6.82 (0.89–52.5)
Tanezumab 2.5 mg + NSAID	2	4	8.76 (1.05–73.4)†
Tanezumab 5 mg + NSAID	0	9	11.11 (1.47–84.0)†
Tanezumab 10 mg + NSAID	2	13	17.50 (2.37–129.4)†

* Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated using the active comparator group as the reference and were adjusted for baseline Kellgren/Lawrence grade, index joint (knee or hip), sex, age, and body mass index. Placebo comparisons were not possible for rapid progression of osteoarthritis (RPOA) and investigator-reported osteonecrosis as there were no events in the placebo group. No RPOA events occurred in the 2.5 mg tanezumab group, so comparison of 2.5 mg tanezumab with active comparator was not possible. One additional episode of type 2 RPOA occurred with a nonsteroidal antiinflammatory drug (NSAID) comparator, and 1 additional episode of type 2 RPOA occurred in a subject with chronic low back pain who was receiving 20 mg tanezumab.
† $P < 0.05$ versus active comparator group.

OSTEONECROSIS

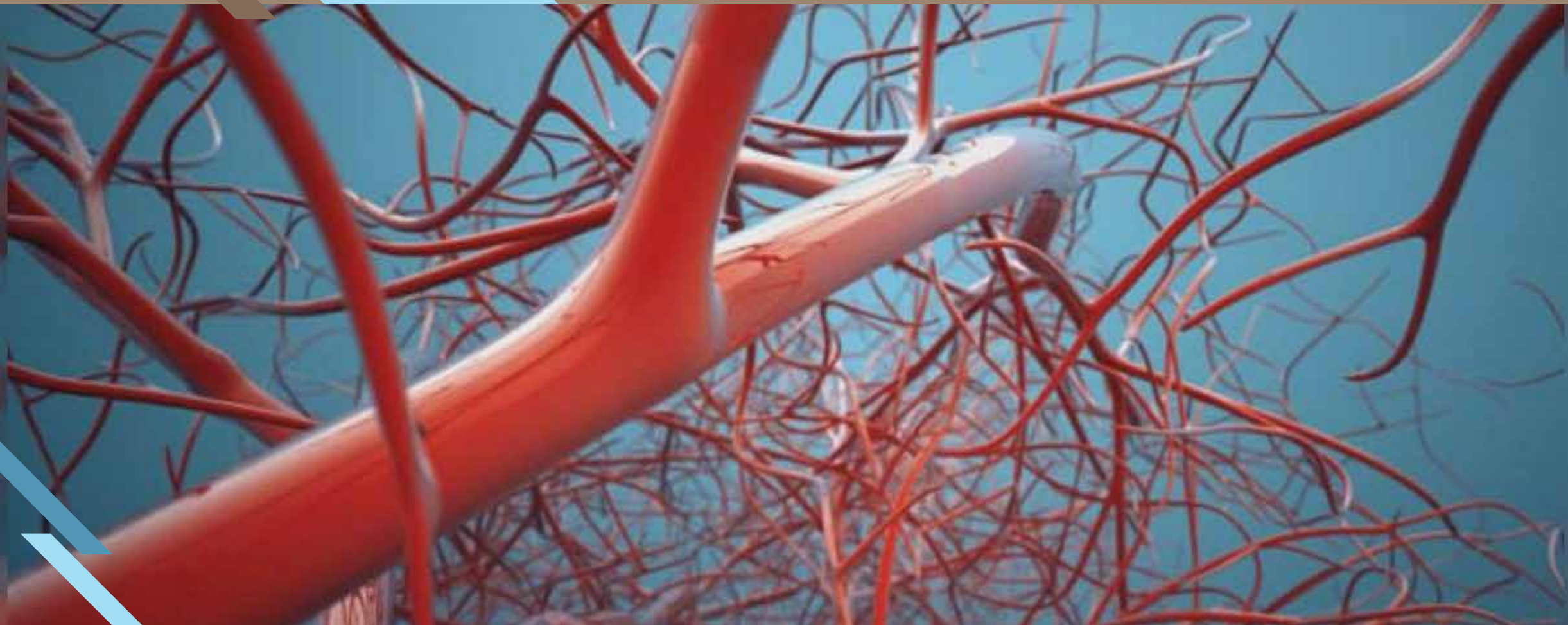
Table 3. HRs for RPOA in phase III OA studies

	RPOA type 1, no. of events	RPOA type 2, no. of events	Treatment comparisons, HR (95% CI)*
Tanezumab 5 mg	3	11	4.10 (0.50–33.4)
Tanezumab 10 mg	4	18	6.82 (0.89–52.5)
Tanezumab 2.5 mg + NSAID	2	4	8.76 (1.05–73.4)†
Tanezumab 5 mg + NSAID	0	9	11.11 (1.47–84.0)†
Tanezumab 10 mg + NSAID	2	13	17.50 (2.37–129.4)†

* Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated using the active comparator group as the reference and were adjusted for baseline Kellgren/Lawrence grade, index joint (knee or hip), sex, age, and body mass index. Placebo comparisons were not possible for rapid progression of osteoarthritis (RPOA) and investigator-reported osteonecrosis as there were no events in the placebo group. No RPOA events occurred in the 2.5 mg tanezumab group, so comparison of 2.5 mg tanezumab with active comparator was not possible. One additional episode of type 2 RPOA occurred with a nonsteroidal antiinflammatory drug (NSAID) comparator, and 1 additional episode of type 2 RPOA occurred in a subject with chronic low back pain who was receiving 20 mg tanezumab.
† $P < 0.05$ versus active comparator group.

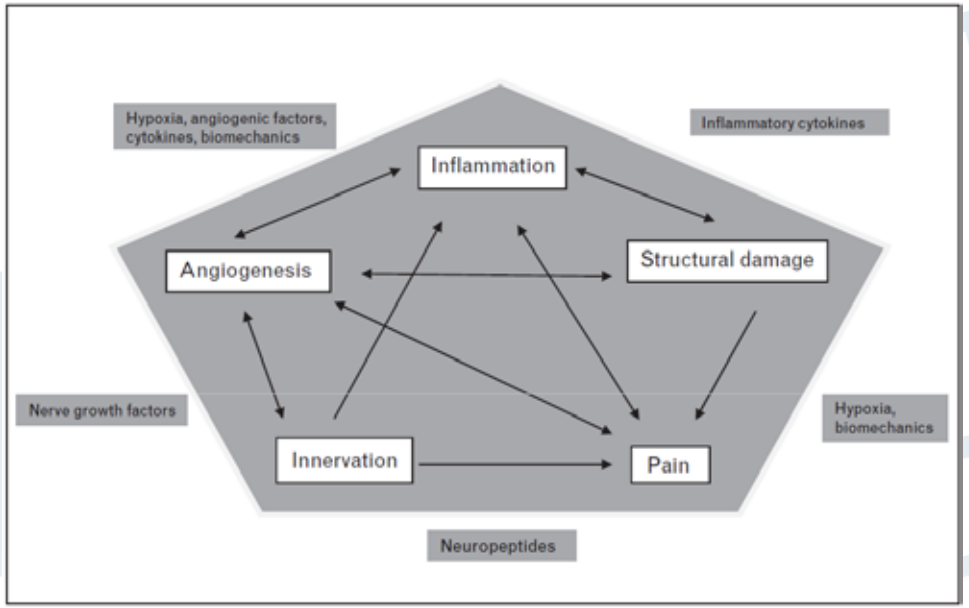
Anti VEGF

Servei de Reumatologia
Hospital del **MAR**



Fisiopatología

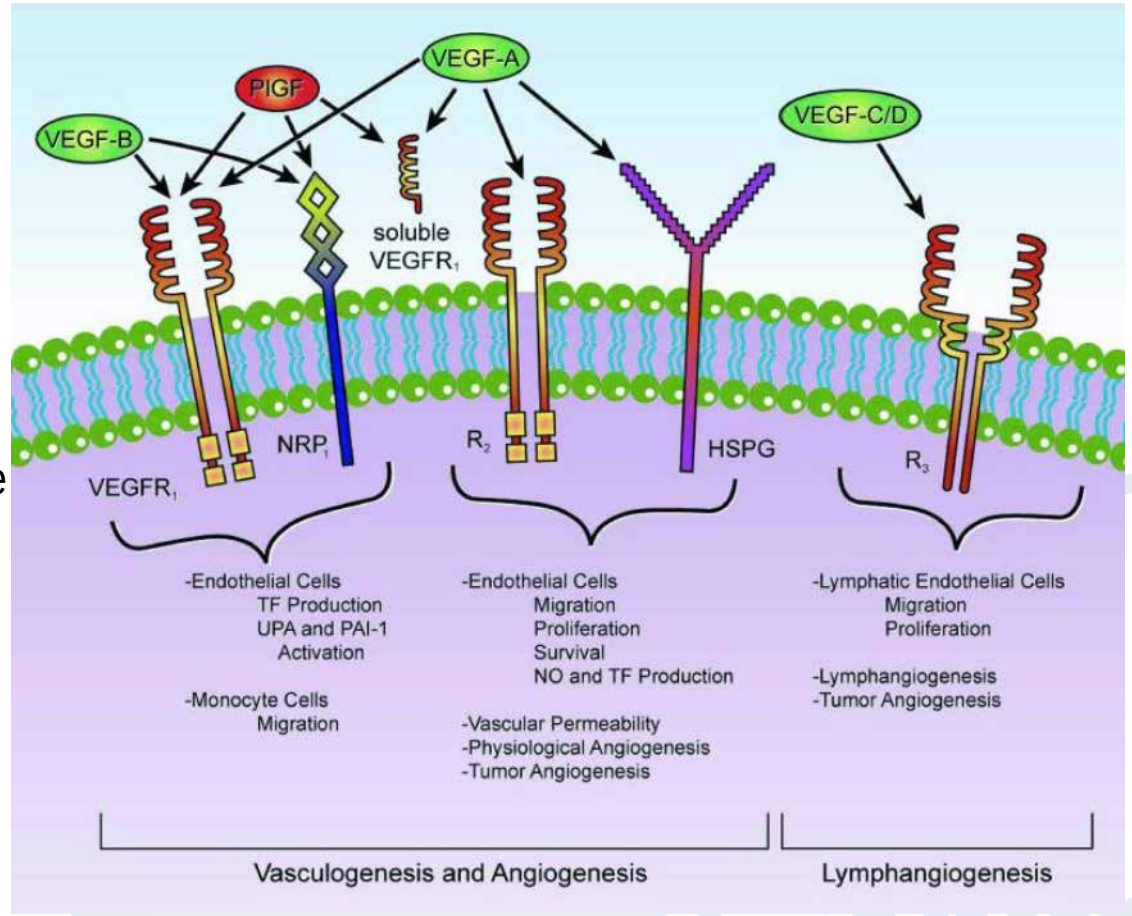
- El cartílago es un tejido avascular, no inervado y sin vasos linfáticos, debido a su composición y estructura.
- Pierde estas características en situaciones:
  - Fisiológicas: Durante el desarrollo, es imprescindible para la inducción de la osificación del cartílago de la placa de crecimiento.
  - En OA: un 60% de los pacientes OA presentan procesos de neovascularización con vasos que provienen del hueso subcondral y atraviesan la tidemark.
- Un tercio de los pacientes con OA presentan procesos de neovascularización también en la membrana sinovial.
- La angiogénesis está asociada a la fisiopatología de la OA ya que:
  - favorece la llegada de células mediadoras de inflamación
  - va acompañada de terminales nerviosas sensoriales y simpáticas
  - Induce la osificación (formación de osteofitos)



Ashraf S, Walsh DA. (2008) Angiogenesis in osteoarthritis. Curr Opin Rheumatol; 20(5):573-80

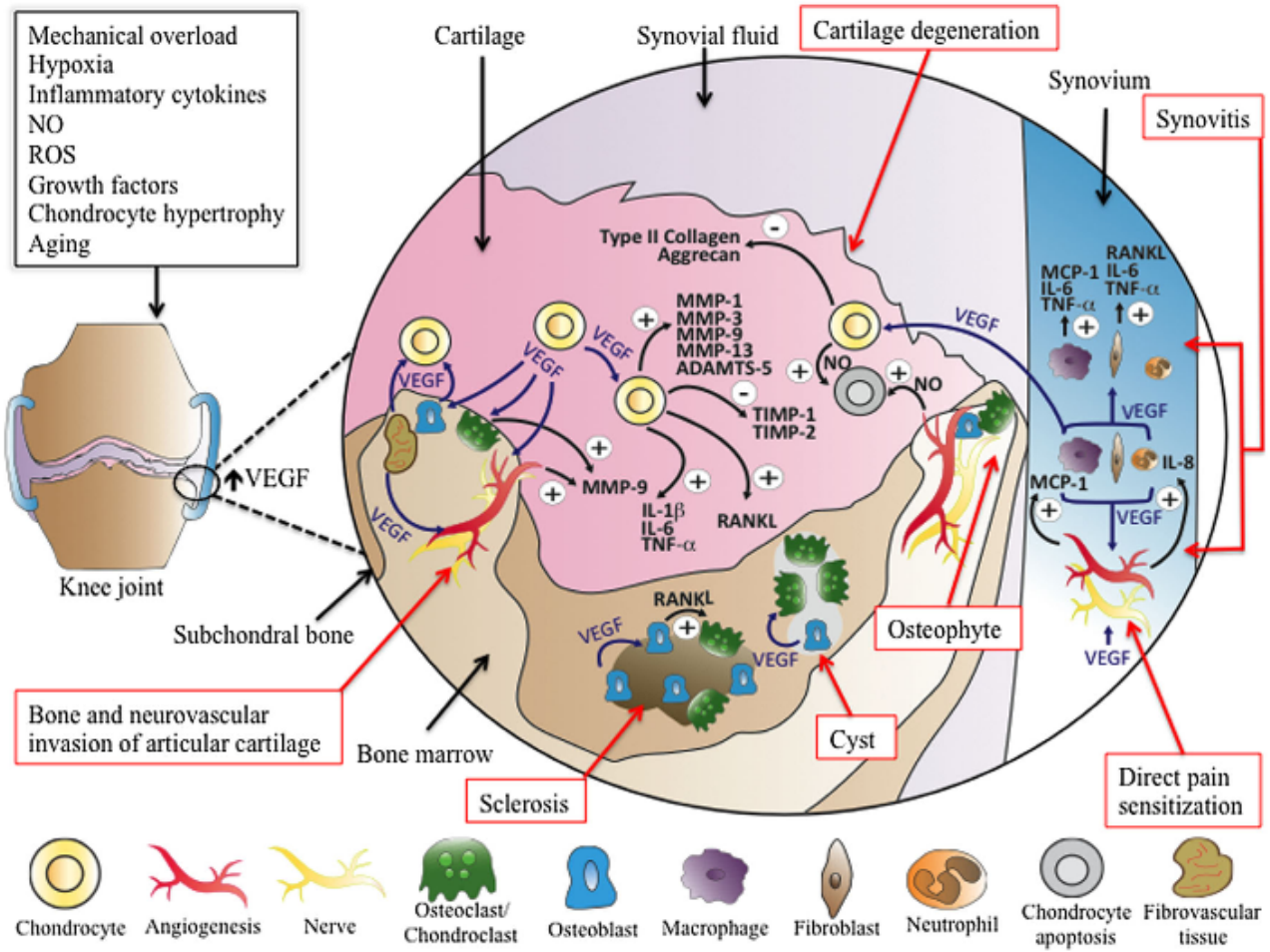
Fisiopatología

- La neovascularización es inducida por un desequilibrio entre factores pro y antiangiogénicos que provocan un incremento de VEGF.
- VEGF es una familia de proteínas conformada por 7 miembros: VEGF/VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F y el factor de crecimiento placental (PIGF).
- VEGF-A es referida clásicamente como VEGF.
- Se une a su receptor tirosin kinasa VEGFR-1 y VEGFR-2, aunque también se puede unir a Neuropilina-1 (receptor de las semaforinas)



Alvarez RH, et al. (2011). Bevacizumab treatment for advanced breast cancer. Oncologist. 2011;16(12):1684-97

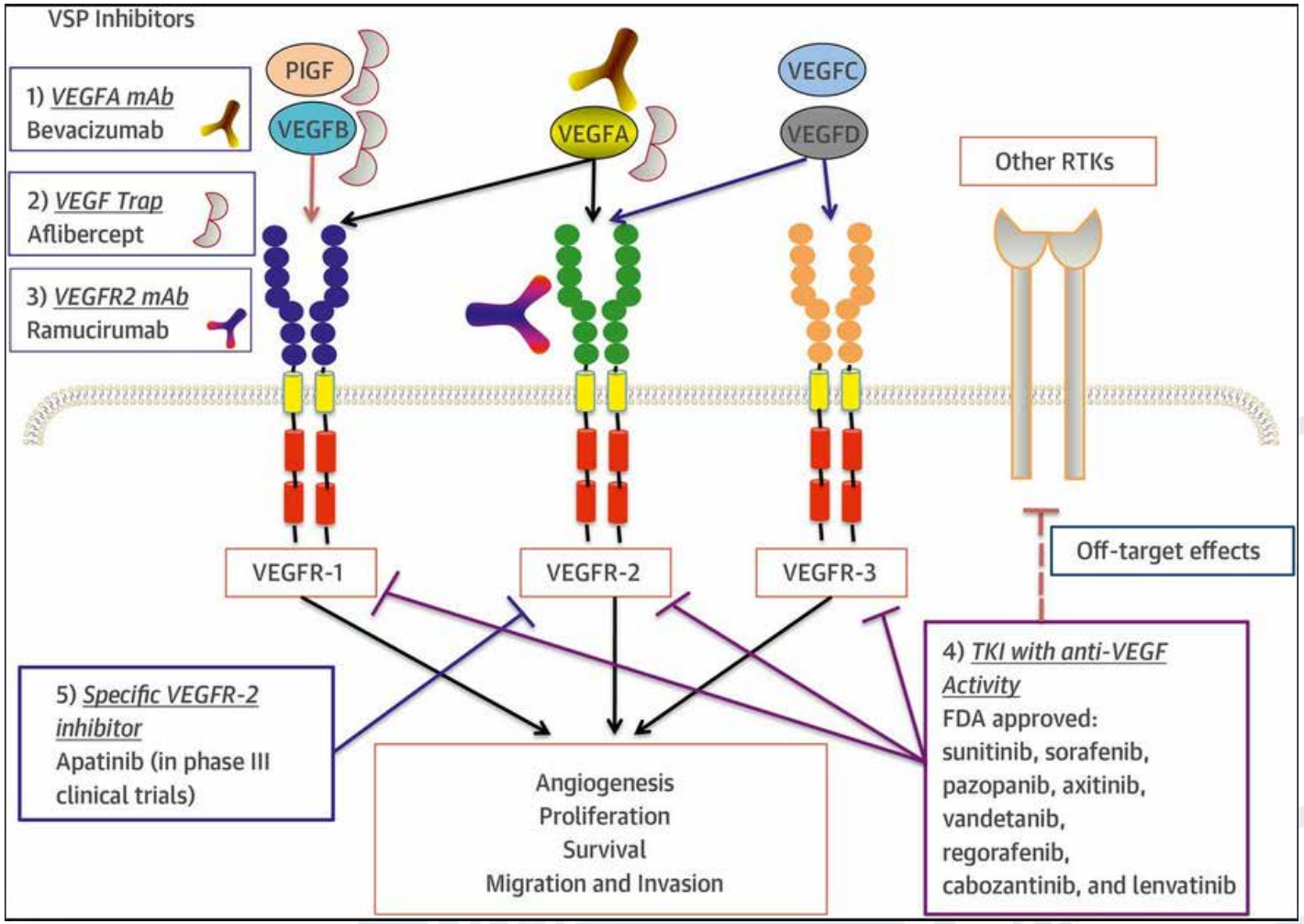
- Diferentes factores implicados en la OA inducen de manera indirecta la producción de VEGF:



Hamilton JL et al (2016) Targeting VEGF and Its Receptors for the Treatment of Osteoarthritis and Associated Pain. J Bone Miner Res. ;31(5):911-204

Fisiopatología

- Bevacizumab (también conocido como Avastina)
- Anticuerpo monoclonal humanizado que reconoce VEGF.
- Es específico de VEGF-A
- Su interacción con VEGF bloquea su acción sobre los receptores VEGFR-1 y VEGFR-2



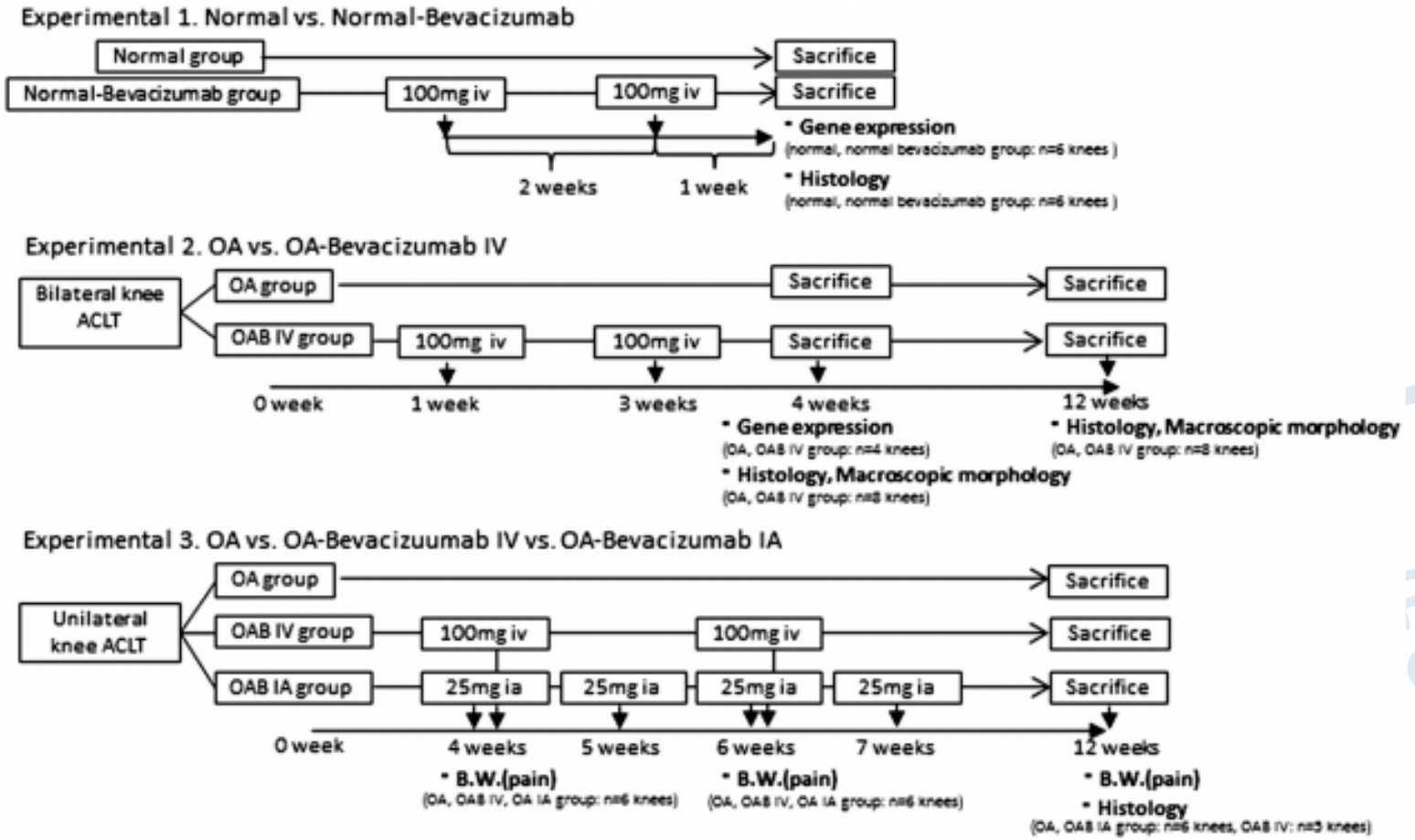
Li W, et al. (2015) Vascular and Metabolic Implications of Novel Targeted Cancer Therapies: Focus on Kinase Inhibitors. J Am Coll Cardiol. 8;66(10):1160-78

Bevacizumab

RESEARCH ARTICLE Open Access

Bevacizumab, an anti-vascular endothelial growth factor antibody, inhibits osteoarthritis

Toshihiro Nagai, Masato Sato*, Miyuki Kobayashi, Munetaka Yokoyama, Yoshiki Tani and Joji Mochida



Bevacizumab, an anti-vascular endotelial growth factor antibody, inhibits osteoarthritis (Nagal et al.).

Bevacizumab

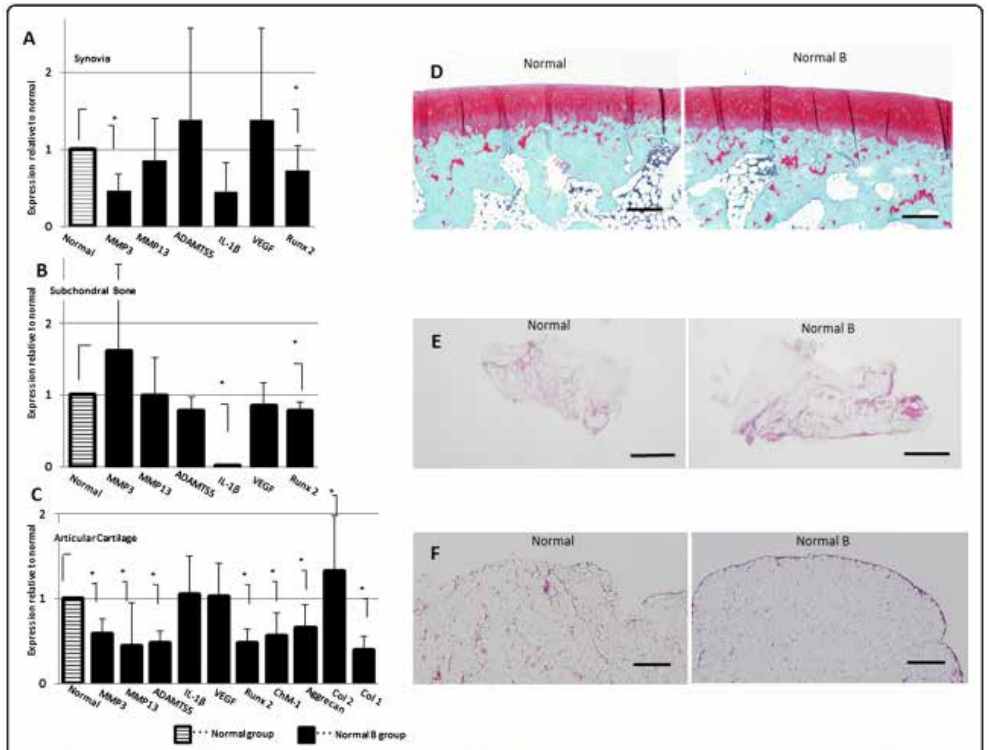


Figure 2 Comparison of gene expression and histology between the normal bevacizumab and normal groups (experiment 1). **(A)** Synovial gene expression. **(B)** Subchondral bone gene expression. **(C)** Articular cartilage gene expression. Gene expression data are expressed as mean ± SD (n = 6 knees). The y-axis is defined as follows: $2^{-\Delta CT}$ normal B target gene/$2^{-\Delta CT}$ normal target gene. *P <0.05 by the Mann-Whitney U-test. **(D)** Representative articular cartilage histology for the normal group (left side) and normal bevacizumab group (right side) stained with Safranin O. **(E)** Representative synovial histology for the normal group (left side) and normal bevacizumab group (right side) stained with H&E. **(F)** Higher magnifications of the image in **(E)** stained with H&E. Histology data were obtained from six knees per group. Bars = 1 mm **(E)**; bars = 300 µm **(D, F)**.

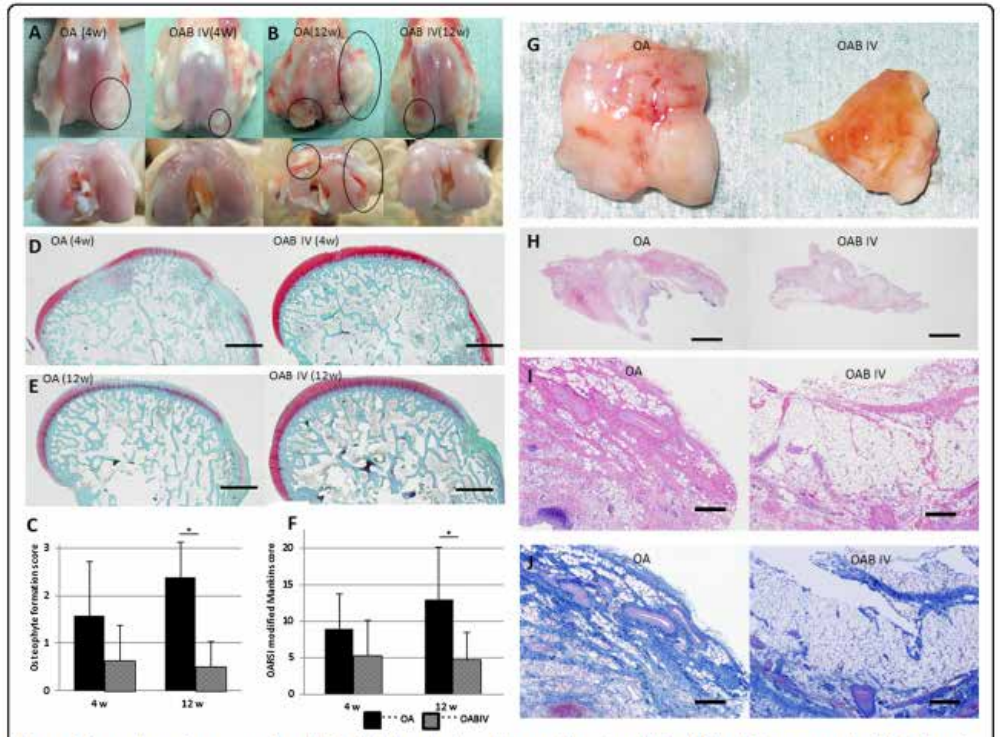


Figure 3 Comparison of macroscopic and histological evaluations between the osteoarthritis (OA) and intravenous administration of bevacizumab in OA (OAB IV) rabbits (experiment 2). **(A)** Macroscopic articular cartilage appearance 4 weeks after anterior cruciate ligament transection (ACLT). **(B)** Macroscopic appearance 12 weeks after ACLT. Circles indicate osteophyte formation. **(C)** Osteophyte formation scores 4 and 12 weeks after ACLT. Data are expressed as mean ± SD (n = 8 knees). Safranin O staining of hyaline cartilage 4 weeks **(D)** and 12 weeks **(E)** after ACLT. **(F)** Osteoarthritis Research Society International histological score 4 and 12 weeks after ACLT. **(G)** Macroscopic synovia appearance 4 weeks after ACLT. **(H)** Representative synovial histology for OA group (left side) and OAB IV group (right side) stained with H&E. Higher magnifications of the image shown in **(H)** stained with HE **(I)** and Masson trichrome **(J)**. Data are expressed as mean ± SD (n = 8 knees). *P <0.05 by the Mann-Whitney U-test. Bars = 1 mm **(D, E, H)**; bars = 300 µm **(I, J)**.

Conclusions: Considering the dosage and potential adverse effects of bevacizumab, the local administration of bevacizumab is a more advantageous approach than systemic administration. Our results suggest that intra-articular bevacizumab may offer a new therapeutic approach for patients with post-traumatic OA.

Bevacizumab

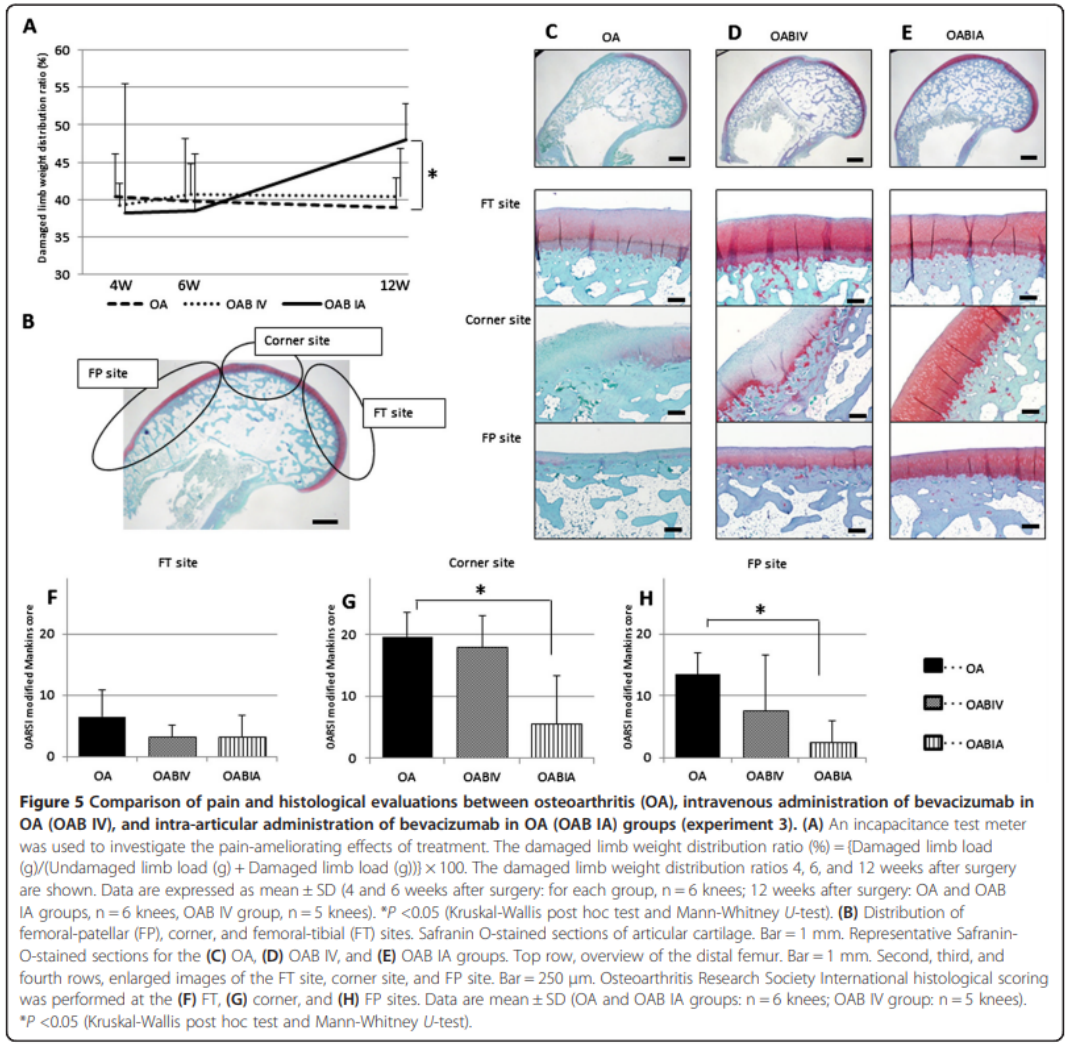


Figure 5 Comparison of pain and histological evaluations between osteoarthritis (OA), intravenous administration of bevacizumab in OA (OAB IV), and intra-articular administration of bevacizumab in OA (OAB IA) groups (experiment 3). (A) An incapacitance test meter was used to investigate the pain-ameliorating effects of treatment. The damaged limb weight distribution ratio (%) = {Damaged limb load (g)/(Undamaged limb load (g) + Damaged limb load (g))} × 100. The damaged limb weight distribution ratios 4, 6, and 12 weeks after surgery are shown. Data are expressed as mean ± SD (4 and 6 weeks after surgery: for each group, n = 6 knees; 12 weeks after surgery: OA and OAB IA groups, n = 6 knees, OAB IV group, n = 5 knees). *P <0.05 (Kruskal-Wallis post hoc test and Mann-Whitney U-test). **(B)** Distribution of femoral-patellar (FP), corner, and femoral-tibial (FT) sites. Safranin O-stained sections of articular cartilage. Bar = 1 mm. Representative Safranin-O-stained sections for the **(C)** OA, **(D)** OAB IV, and **(E)** OAB IA groups. Top row, overview of the distal femur. Bar = 1 mm. Second, third, and fourth rows, enlarged images of the FT site, corner site, and FP site. Bar = 250 µm. Osteoarthritis Research Society International histological scoring was performed at the **(F)** FT, **(G)** corner, and **(H)** FP sites. Data are mean ± SD (OA and OAB IA groups: n = 6 knees; OAB IV group: n = 5 knees). *P <0.05 (Kruskal-Wallis post hoc test and Mann-Whitney U-test).

Tissue Eng Part B Rev. 2016 Oct;22(5):341-357. Epub 2016 Mar 31.

Repositioning Bevacizumab: A Promising Therapeutic Strategy for Cartilage Regeneration.

Lee S[1], Nemeño JG[1], Lee JI[1,2].

Author information

TABLE 4. BEVACIZUMAB AND ITS EFFECTS ON CARTILAGE REGENERATION

Year of publication	*Drugs (dosage) and mode of administration*	*Reported results*	*Type of study*		*References (authors)*
			In vitro	In vivo *(animal species)*	
2010	Bevacizumab (40 mg/kg) IV	(i) Significant cartilage regeneration in rheumatoid arthritis (ii) IV administration of bevacizumab contributes to better repair of articular cartilage in an osteochondral defect model (iii) Chondromodulin expression on the repair site	O	O (rabbit)	86
2013	Bevacizumab (30 mg/kg) and Etanercept (6 mg/kg) IV	(i) Improved stable nose cartilage formation in *in vivo* model (ii) Therapeutic efficiency of bevacizumab has no significant difference with Etanercept in regenerating type II collagen-induced arthritis (iii) Bevacizumab is a promising therapeutic agent for rheumatoid arthritis.	O	O (rat)	88
2013	Scaffold-based implantation, sodium hyaluronate (10 mg/mL), fibrinogen (20 mg/mL), and bevacizumab (3.75 mg/mL) SC	(i) Bevacizumab efficiently blocked angiogenesis and cell infiltration after subcutaneous implantation of release from nasal cartilage-loaded scaffolds (ii) Bevacizumab counteracted *in vitro* endothelial cell proliferation and macrophage migration (iii) Bevacizumab improved cartilage regeneration by MACI	O	O (nude mice)	138
2014	Bevacizumab IA (25 mg/kg) and IV (100 mg/kg)	(i) Bevacizumab enhanced type 2 collagen expression in the articular cartilage (ii) Bevacizumab promoted cartilage regeneration with reduced osteophyte formation (iii) IA administration of bevacizumab increased the expression of chondrogenic genes compared to systemic IV injection (iv) IA localized administration of bevacizumab is a more effective, safe, and novel therapeutic strategy for OA	O	O (rabbit)	87

MACI, matrix-induced ACI.

Conclusiones

- NGF es una molecula clave en la regulación del dolor en OA
- Tanezumab y fasinumab han demostrado ser efectivos para el tratamiento del dolor moderado a grave de la OA de rodilla y cadera
- Las artrosis rápidamente progresivas atribuidas a los anti-NGF están relacionadas con las dosis más altas y en particular a la asociación de anti-NGF i AINEs
- En el caso de Tanezumab existen dudas sobre si la reducción de dosis podría determinar la eficacia del fármaco
- La angiogénesis es determinante en los cambios estructurales y los síntomas de la artrosis
- De totas las moléculas autorizadas para el tratamiento de la angiogénesis bevacizumab es la que parece llamada a jugar un papel en el tratamiento de la artrosis
- Las etapas tempranas en la investigación del fármaco y la complejidad del fenómeno angiogénico nos obligan a ser prudentes a la hora de extraer conclusiones

Gracias por la Atención

Servei de Reumatologia
Hospital del **MAR**