

# What is New in Behçet's syndrome?

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# Disclosures

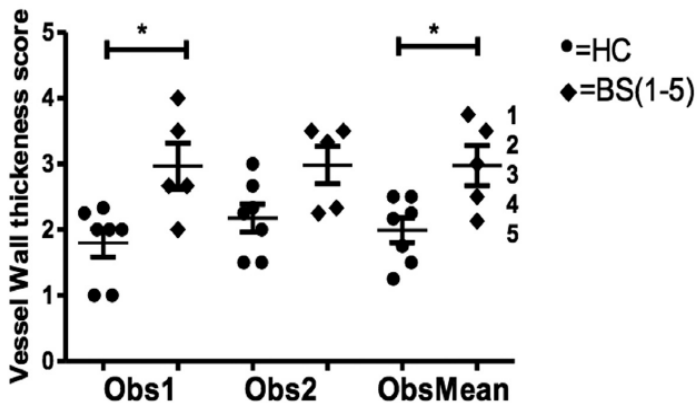
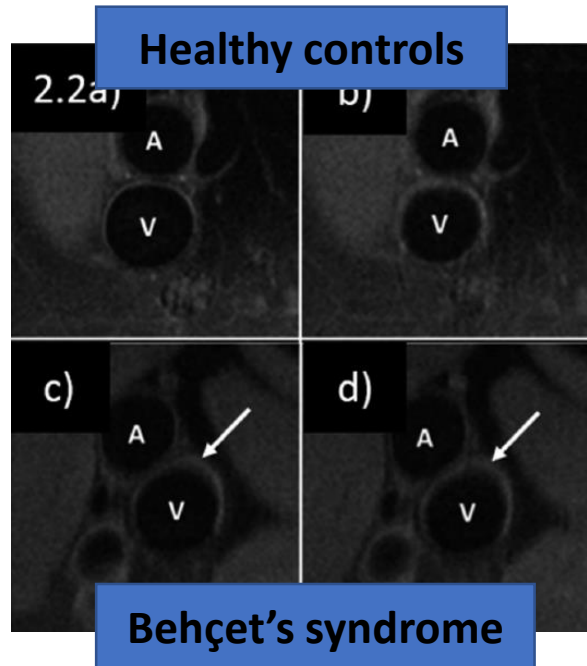
- Abbvie - research grant, speaker
- Amgen - speaker
- Bayer – speaker, advisory board member
- Celgene – research grant, speaker, advisory board member
- Lilly – research grant
- Johnson & Johnson - advisory board member
- Novartis - speaker
- Silk Road Therapeutics - research grant
- UCB Pharma - research grant, speaker

# Outline

- **What is new in diagnosis and disease assessment?**
  - Vein wall thickness for diagnosis?
  - A Core Set of Domains for Behçet's syndrome
- **What is new in treatment?**
  - Different aspects of TNF inhibitor use
  - Effect of anticoagulation on post-thrombotic syndrome
  - Apremilast for non-oral ulcer manifestations

# Increased vein wall thickness in Behçet's syndrome

## MRI



Ambrose et al. Clin Exp Rheum 2014

## USG

	BS with vascular inv.	BS no vascular inv.	Healthy controls	P value
Right CFV	0.91±0.67	0.69±0.15	0.57±0.11	0.001
Right SFV	0.79±0.38	0.60±0.11	0.51±0.9	<0.001
Right VSM	0.60±0.22	0.52±0.11	0.43±0.07	<0.001

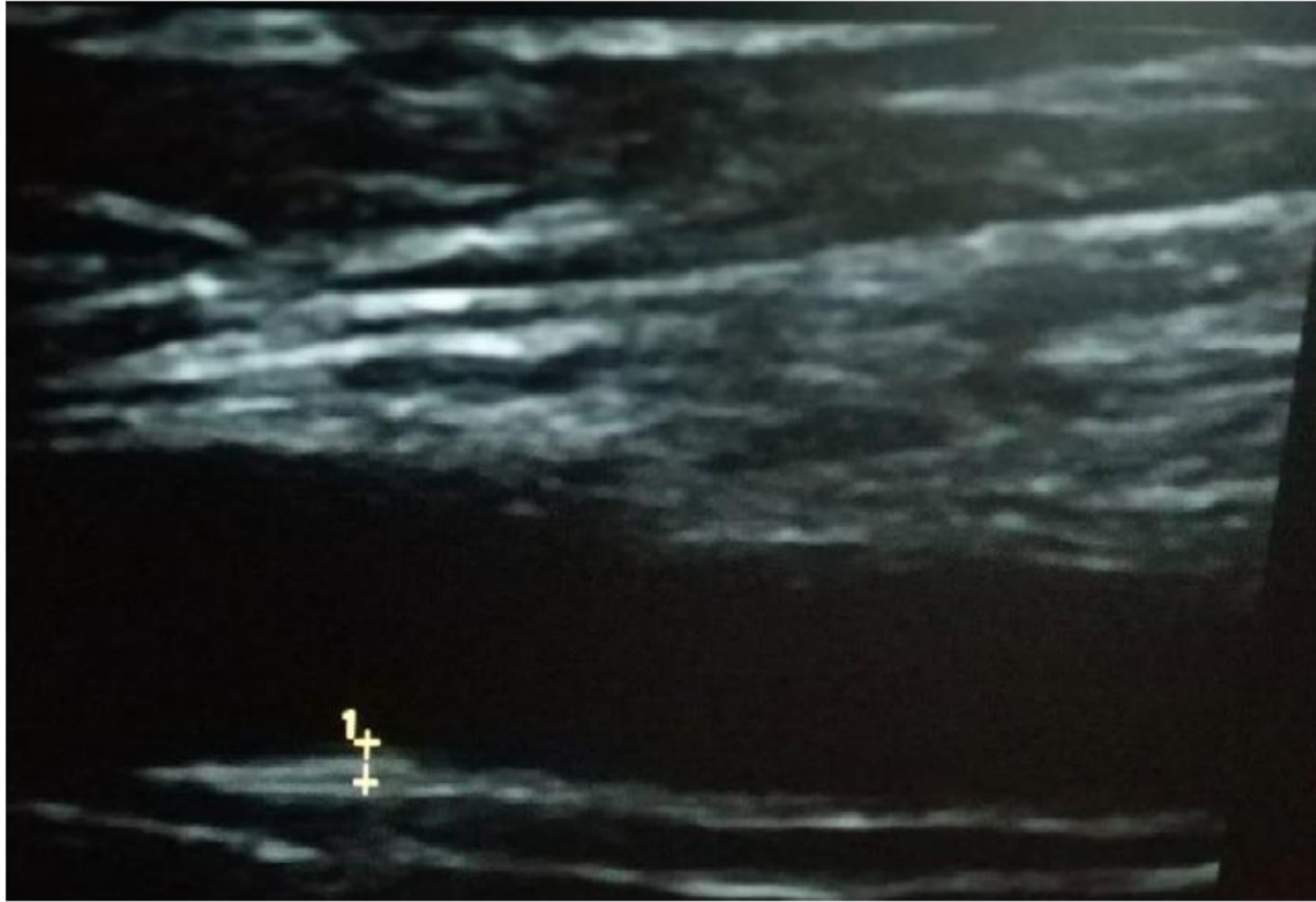
Vein wall thickness is increased among BS patients compared to healthy controls and even more so among BS patients with a history of thrombosis

Seyahi et al. J Vasc Surg Venous Lymphat Disord. 2019

	Behçet's syndrome	Ankylosing spondylitis	Healthy controls	P value
Right CFV	0.8 (0.04-1.8)	0.3 (0.1-0.6)	0.25 (0.06-0.4)	<0.001
Right VSM	3.1 (0-6.4)	2.5 (1.1-3.5)	2.1 (1.3-3.5)	<0.001

Vein wall thickness is increased among BS patients compared to ankylosing spondylitis and healthy controls

Alibaz-Oner et al. Clin Rheumatol. 2019

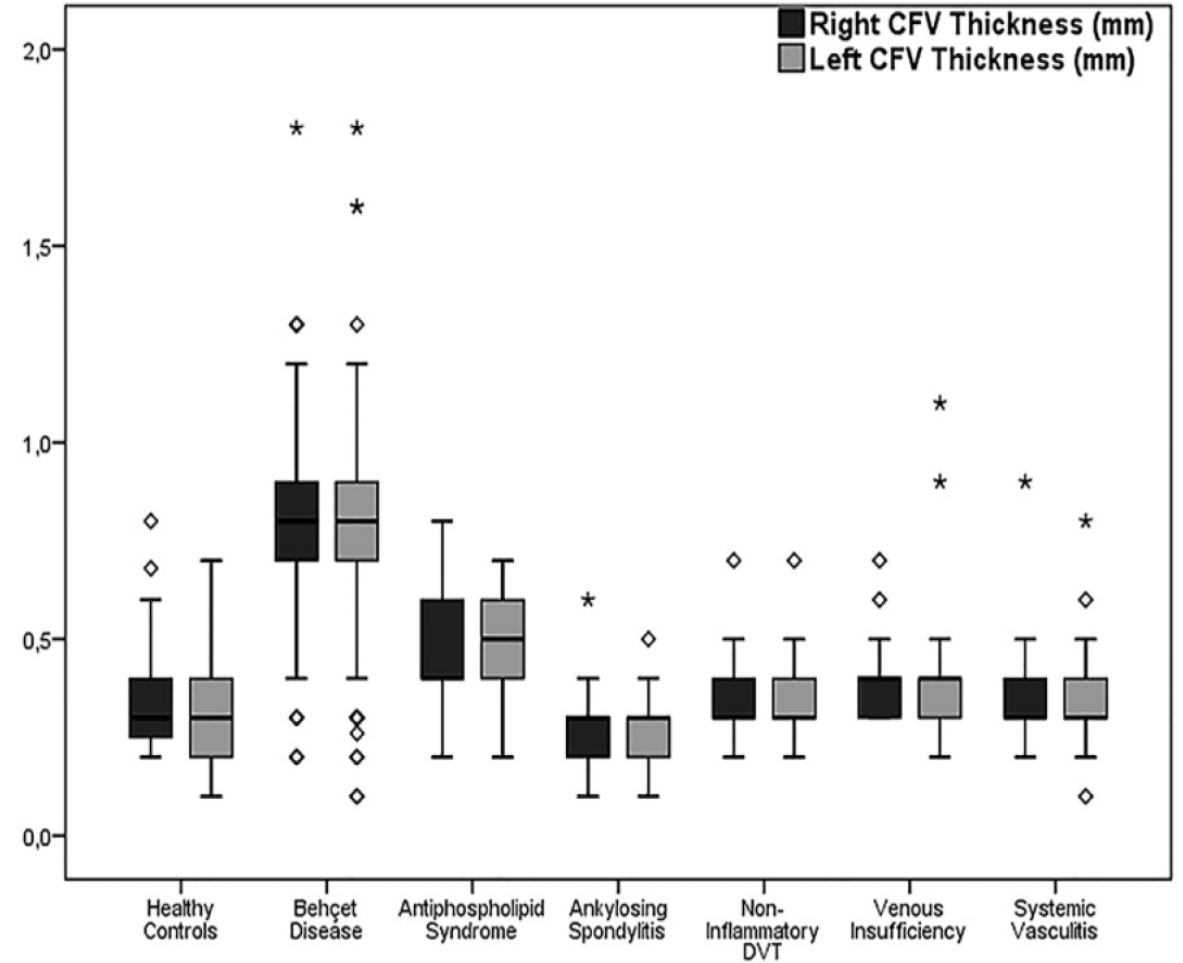
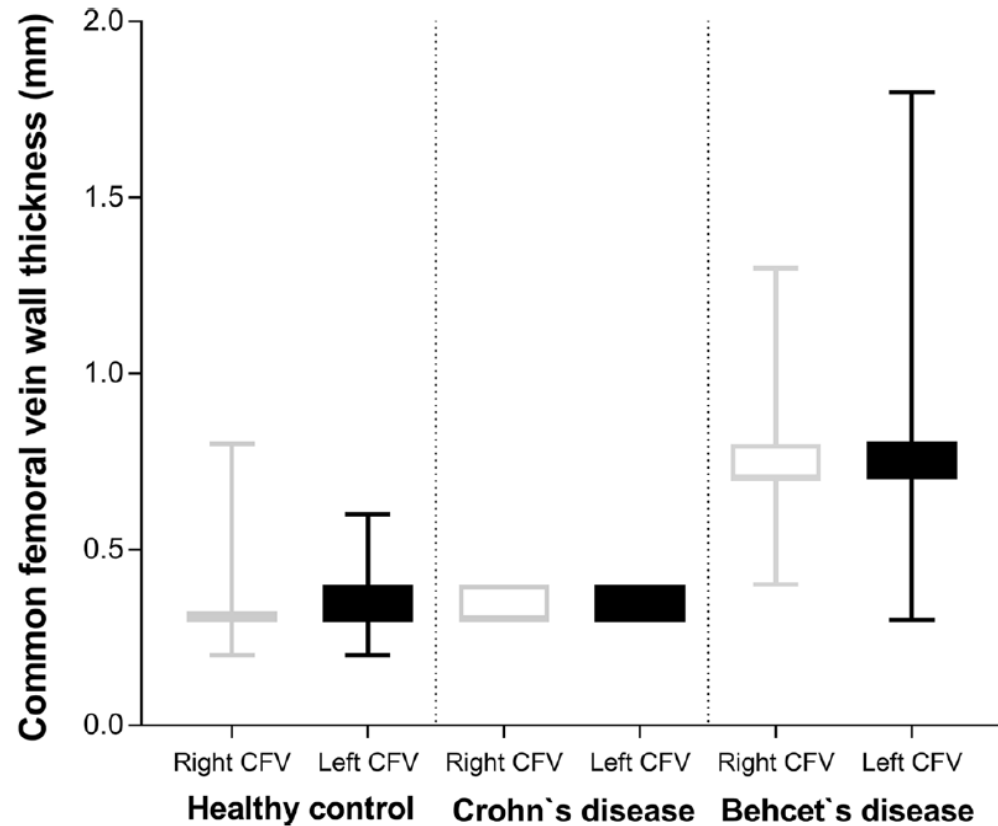


**FIGURE 1** B-mode ultrasound picture of a common femoral vein on a longitudinal plane showing increased venous wall thickness in a patient with Behçet's disease






Study	Study groups (n; M/F)	Mean age $\pm$ SD, years	VWT (CFV), mean $\pm$ SD
<b>Alibaz-Oner 2021</b>	BS (152; 110 M/42 F)	35.1 $\pm$ 8.0	0.77 $\pm$ 0.2
	AS (27; 27 M)	30.5 $\pm$ 4.5	0.27 $\pm$ 0.1
	Vasculitis (23; 12 M/ 11 F)	32.2 $\pm$ 7.0	0.34 $\pm$ 0.1
	Venous insuf. (29; 15 M/14 F)	37.6 $\pm$ 9.0	0.38 $\pm$ 0.1
	APS (43; 12 M/ 31F)	39.0 $\pm$ 10.0	0.49 $\pm$ 0.2
	Non-inflam. DVT (25; 16M/9 F)	42.1 $\pm$ 9.0	0.35 $\pm$ 0.1
	HC (51; 40 M/11 F)	30.3 $\pm$ 6.0	0.34 $\pm$ 0.1
<b>Alibaz-Oner 2021</b>	BS (69; 33 M/36 F)	37.9 $\pm$ 8.0	0.76 $\pm$ 0.2
	CD (38; 19M/19 F)	41.7 $\pm$ 13.0	0.33 $\pm$ 0.1
	HC (38; 21 M/17 F)	37.1 $\pm$ 7.0	0.34 $\pm$ 0.1
<b>Kaymaz, 2021</b>	BS vascular (25; 16 M/ 9 F)	38.0 $\pm$ 8.9	0.85 $\pm$ 0.3
	BS w/o vascular (38; 25 M/ 13F)	38.1 $\pm$ 11.2	0.83 $\pm$ 0.3
	HC (30; 14 M/ 16 F)	40.3 $\pm$ 10.0	0.52 $\pm$ 0.15
<b>Tezcan, 2022</b>	BS (54; 32 M/ 22 F)	38.96 $\pm$ 10.11	0.83 $\pm$ 0.26
	HC (52; 32 M/ 20 F)	36.90 $\pm$ 12.58	0.43 $\pm$ 0.11

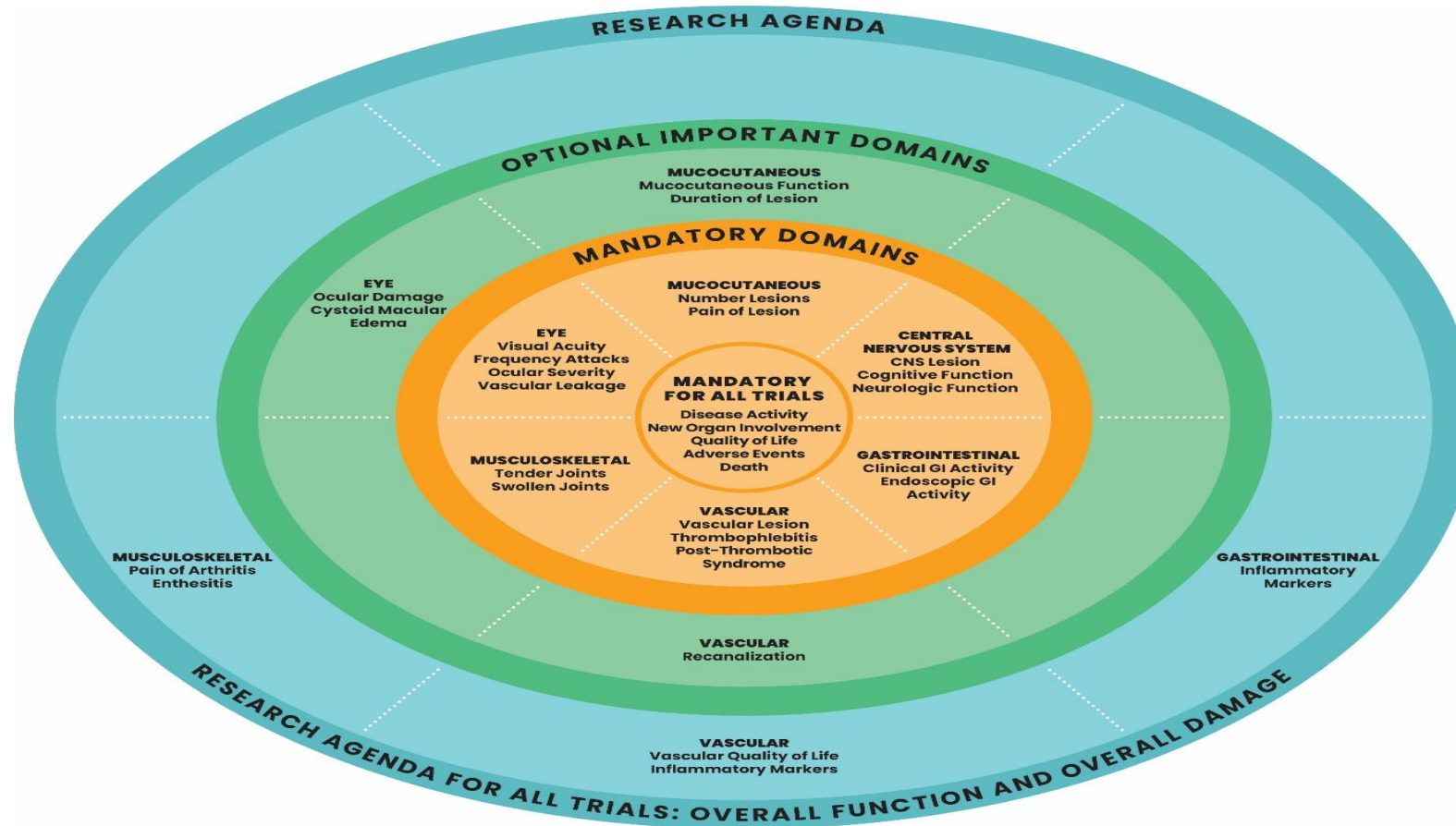
# Can femoral vein wall thickness be used as a diagnostic tool?

**Fig. 1** Distribution of common femoral vein (CFV) thicknesses in study groups  
The asterisk (\*) and lozenge (◇) symbols are representing the extreme values in the groups.

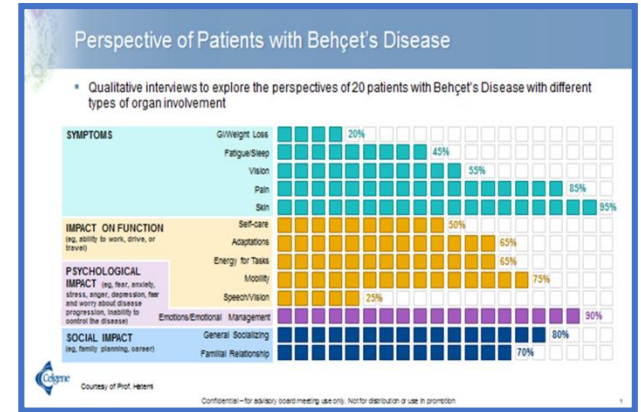
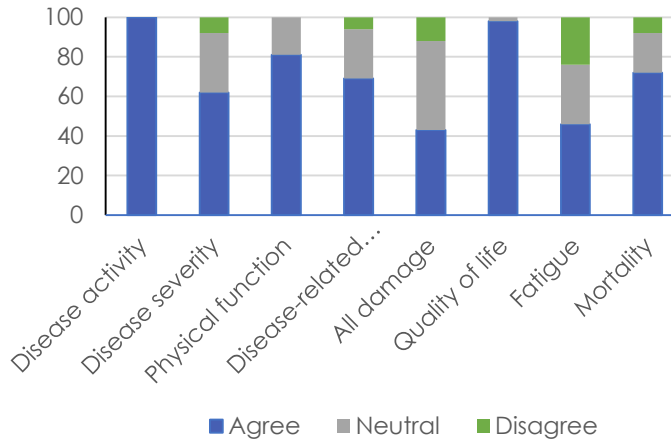
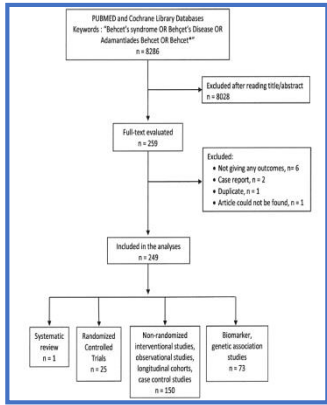


# Core Set of Domains for Outcome Measures in Behçet's Syndrome

Gülen Hatemi,<sup>1</sup>  Alexa Meara,<sup>2</sup>  Yesim Özgüler,<sup>1</sup>  Haner Direskeneli,<sup>3</sup> Alfred Mahr,<sup>4</sup>  Beverly Shea,<sup>5</sup> Esen Cam,<sup>6</sup> Ahmet Gul,<sup>7</sup> Yusuf Yazici,<sup>8</sup> Peter Tugwell,<sup>9</sup> Hasan Yazici,<sup>10</sup> and Peter A. Merkel,<sup>11</sup>  for the Outcome Measures in Rheumatology Behçet's Syndrome Working Group



# Developing a «Core Set» of Domains for Behçet's Syndrome



Systematic review of all outcomes used

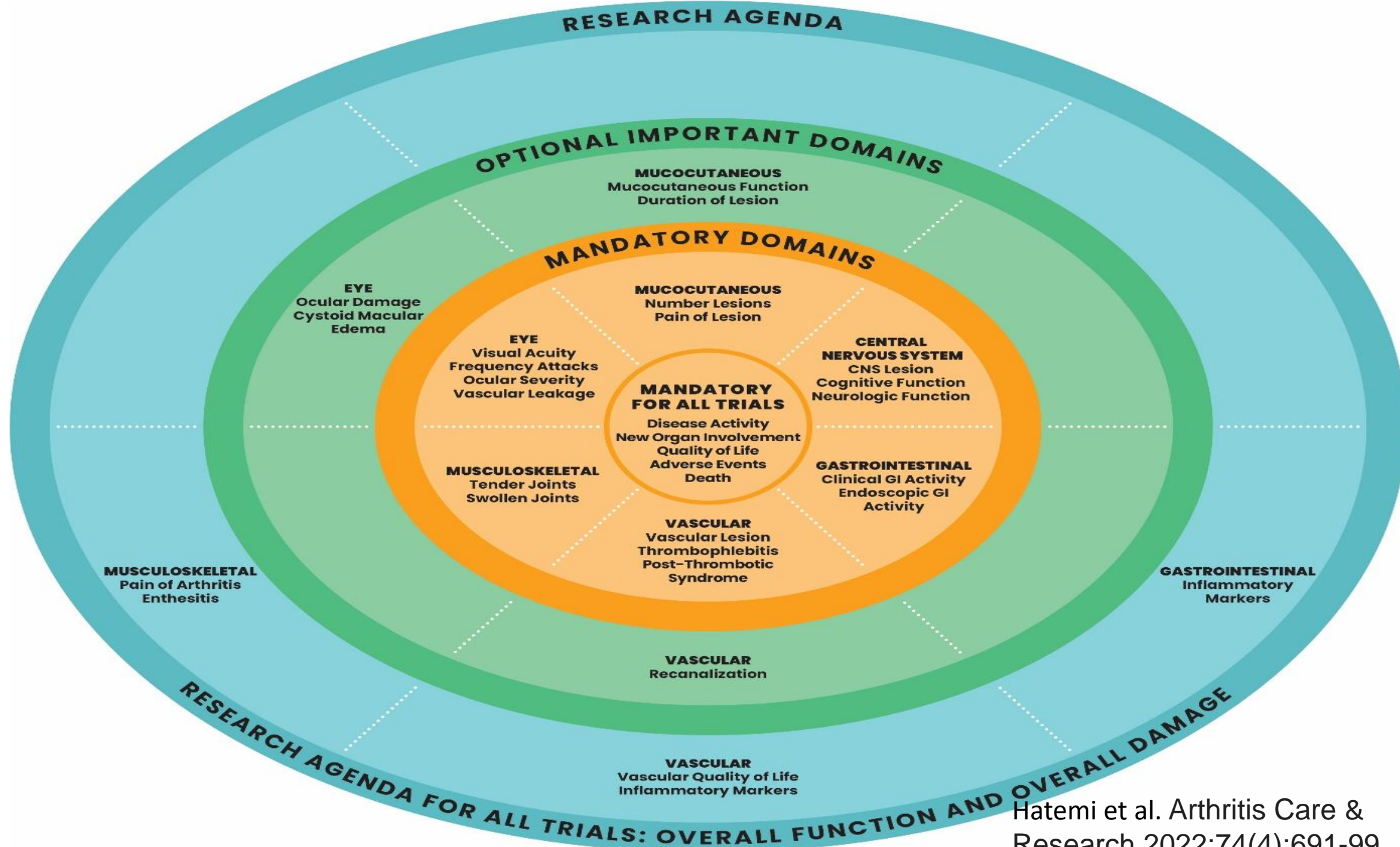
Asked the experts

Asked the patients

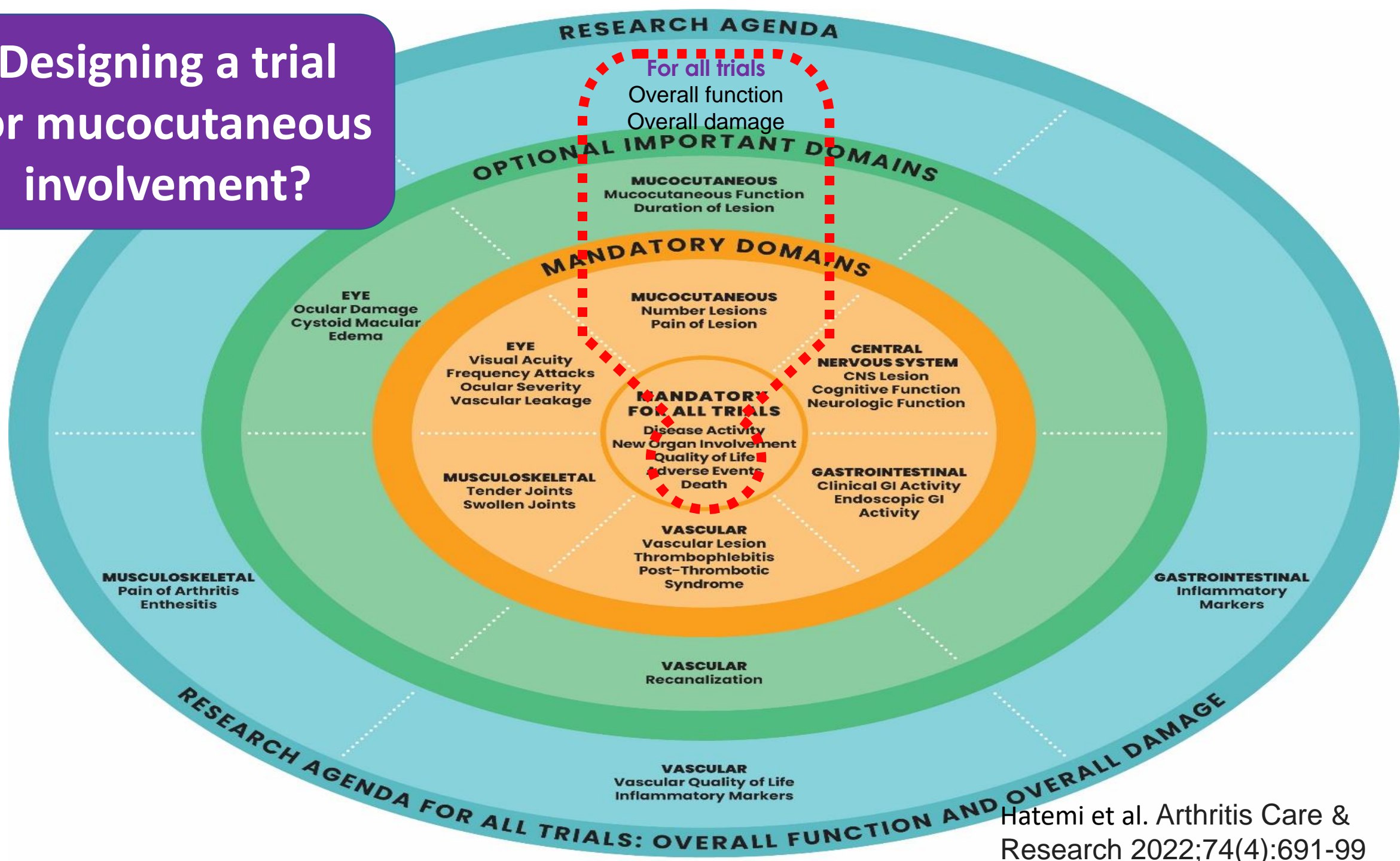


Core Set of Domains

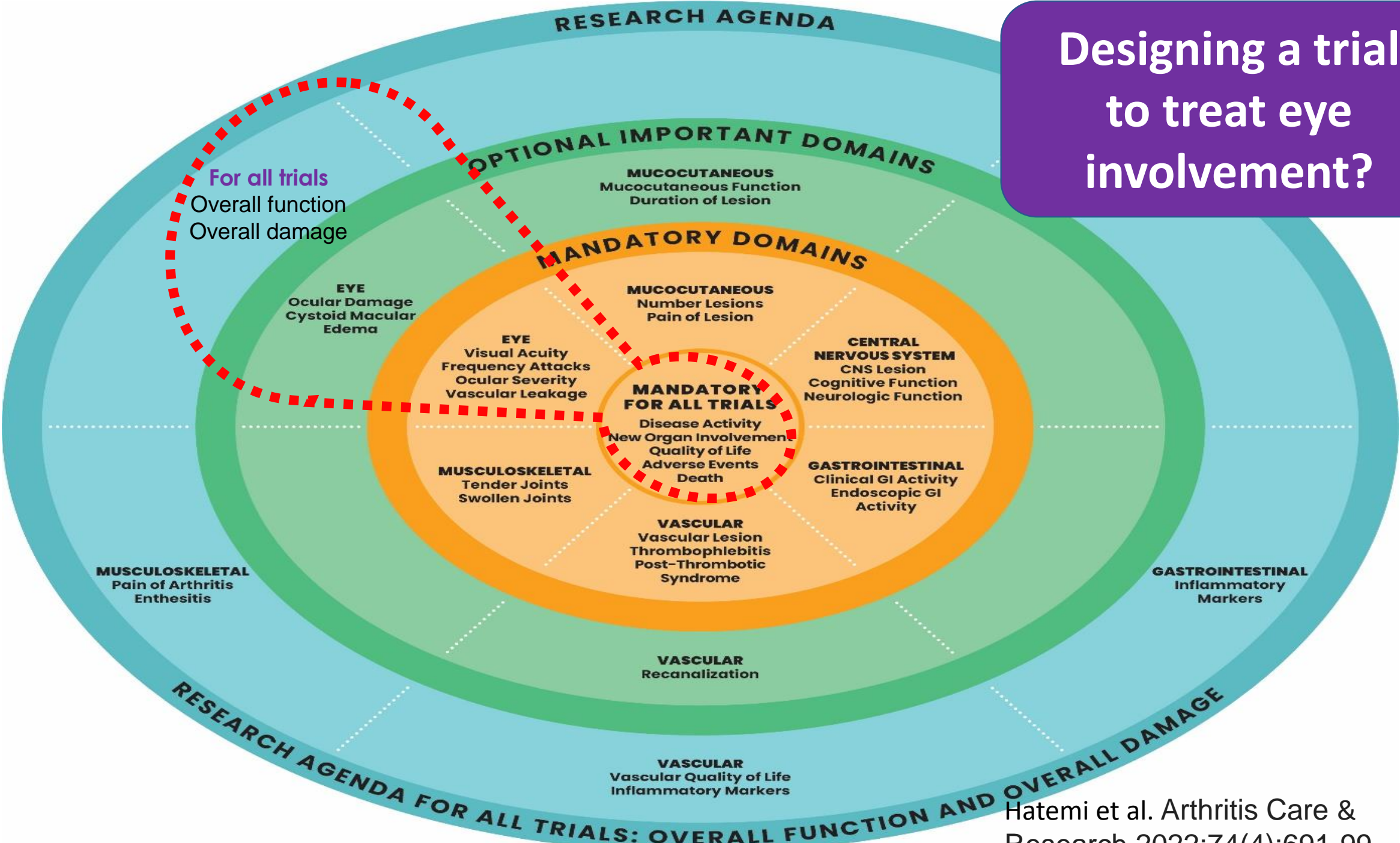
A 3 Step Delphi among physicians and patients



Designing a trial for mucocutaneous involvement?



Designing a trial to treat eye involvement?



# Instruments for the assessment of disease activity

## Overall disease activity instruments

- Behçet's disease current activity form
- Behçet's Syndrome Activity Scale
- Clinical Disease Activity Index
- Clinical Manifestations Index
- Iranian BD Dynamic Activity Measure
- 1994 Criteria for Disease Activity

## Organ/system specific instruments

- Developed for Behçet's syndrome
  - Mucocutaneous Activity Index
  - Ocular attack score 24
  - The Angiography Scoring for Uveitis Working Group scoring system
  - Disease activity index for intestinal Behçet's disease
- Developed for similar diseases
  - SUN kriterleri
  - Crohn's disease activity index

# Questions regarding TNF inhibitor use in Behçet's syndrome

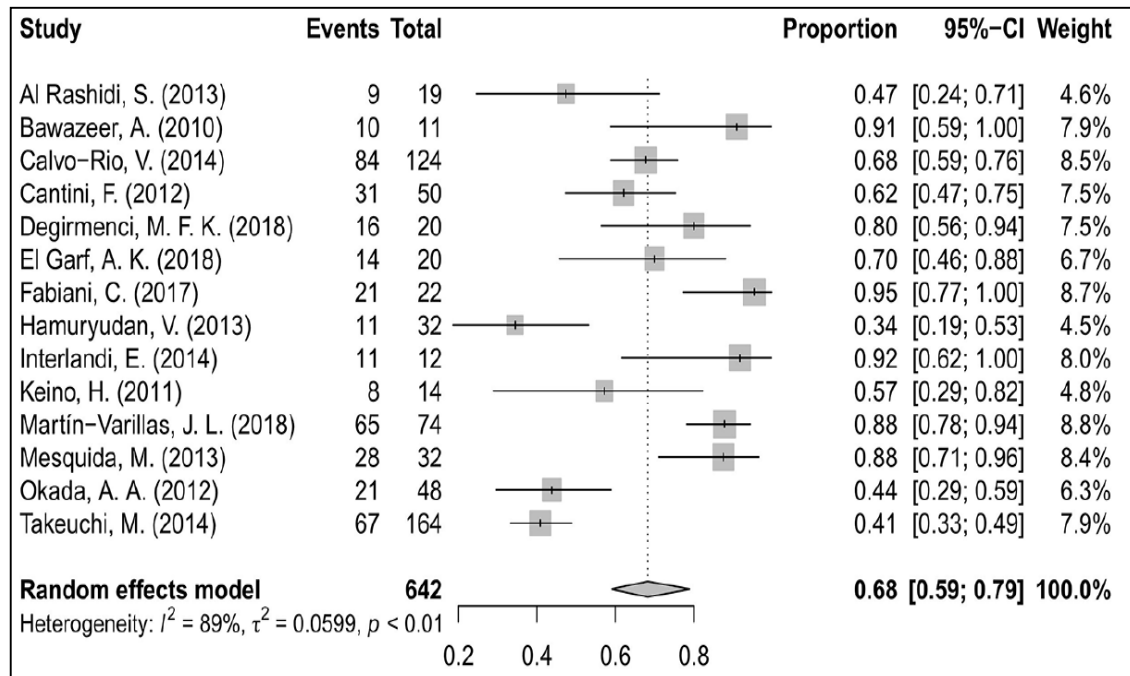
- Any differences between TNF inhibitors?
- Early TNFi use or step-up treatment?
- Can TNFi replace cyclophosphamide for vascular involvement?
- Do TNFi prevent new organ involvement?

	Skin and mucosa	Arthritis	Uveitis	Vascular involvement	CNS involvement	Gastrointest involvement
<b>Colchicine</b>						
<b>PDE-4</b>						
<b>Azathioprine</b>						
<b>Cyclosporine-A</b>						
<b>Cyclophosphamide</b>						
<b>Interferon-alpha</b>						
<b>TNF inhibitors</b>						
<b>IL-1 inhibitors</b>			ANA CAN	GEV		
<b>IL-6 inhibitor</b>						
<b>IL-17 inhibitor</b>						
<b>IL-23 inhibitor</b>						

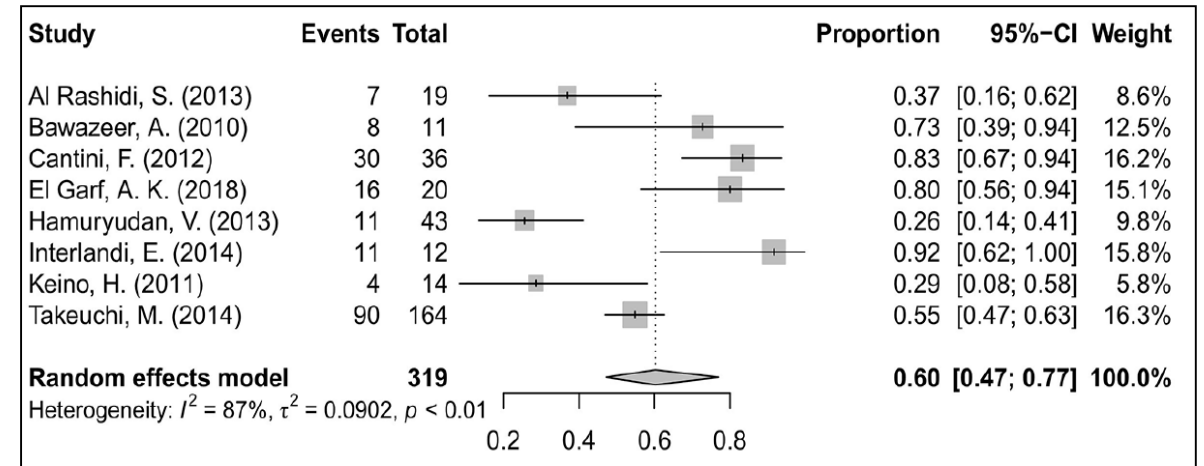
	Effective based on RCTs		Contraversial / inconclusive data
	Beneficial based on non-randomized data		Reported to cause relapses
	Not effective		Not evaluated

# TNF inhibitors for Behçet's Uveitis

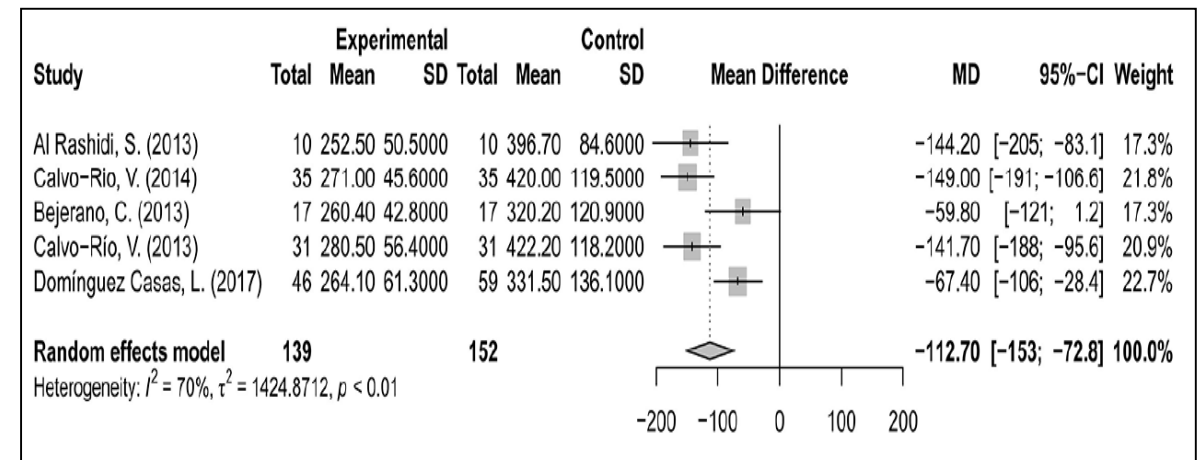
- A meta-analysis of 18 un-controlled studies
- 22 patients (2.6%) experienced severe adverse events - infusion reactions, pneumonia, bacteremia, tuberculosis, melanoma, lymphoma



**Remission rate of inflammation**



**Improvement in visual acuity**



**Reduction in macular thickness**

# Comparison of infliximab and adalimumab for Behçet's uveitis

	Atienza-Mateo B. et al., 2019		Fabiani C. et al., 2019	
	IFX	ADA	IFX	ADA
<b>n of patients</b>	103 (55 M/48 F)	74 (39 M/ 35 F)	41	66
<b>Previous treatment (%)</b>				
Corticosteroid	95	88	100	100
Cyclosporine	75	78	23	27
Azathioprine	57	42	8	17
Methotraxate	44	42	12	20
<b>Combination with cDMARD %</b>				
Cyclosporine	76.5	70.3	48.8	46.7
Azathioprine	41.1	55.7	40	22.6
Methotraxate	21.8	19.2	15	29
MMF	33.3	21.1	30	35.4
	1.3	3.8	20	3.2
<b>Treatment outcomes at mo 12</b>				
Improvement of ACI %	78.2	92.3	NA	NA
Improvement of vitritis %	79.0 <sup>†</sup>	93.3 <sup>†</sup>	NA	NA
Improvement of RV %	97	95	86.3	71.4
Macular thickness	264.9±59.7	250.6±36.9	NA***	NA***
BCVA	0.67±0.34 <sup>‡</sup>	0.81±0.26 <sup>‡</sup>	0.4±0.0	0.4±0.11
Decrease of uveitis attack%	NA	NA	84.2	66.7
Drug retention rate %	85.0 <sup>§</sup>	95.2 <sup>§</sup>	87.8	79.8
Severe AE/toxicity	8 (7.8)	4 (3.9)	NA	NA

# Lower Relapses Rate With Infliximab Versus Adalimumab in Sight-Threatening Uveitis: A Multicenter Study of 330 Patients



GEORGINA MAALOUF<sup>1</sup>, ANAÏS ANDRILLON<sup>2</sup>, MATHILDE LECLERCQ<sup>3</sup>, PASCAL SÈVE, PHILIP BIELEFELD, JULIE GUEUDRY, THOMAS SENÉ, CHERIF TITAH, THOMAS MOULINET, BÉNÉDICTE ROUVIÈRE, DAMIEN SÈNE, ANNE-CLAIRE DESBOIS, FANNY DOMONT, SARA TOUHAMI, THOMAS THIBAUT, CAROLLA EL CHAMIEH, PATRICE CACOUB, LAURENT KODJIKIAN, LUCIE BIARD, BAHRAM BODAGHI, AND DAVID SAADOUN

**Am J Ophthalmol 2022;238: 173–180.**

Variable	All Patients, Median	Adalimumab	Infliximab
Total	330	167	163
Sex			
Female	181 (54.8)	94 (56.3)	87 (53.4)
Juvenile idiopathic arthritis	19 (5.8)	11 (6.6)	8 (4.9)
Behçet disease	89 (27.0)	25 (15.0)	64 (39.3)
Birdshot chorioretinopathy	38 (11.5)	29 (17.4)	9 (5.5)
Idiopathic	125 (37.9)	74 (44.3)	51 (31.3)
Sarcoidosis	18 (5.5)	13 (7.8)	8 (4.9)
Spondylo-arthritis	11 (3.3)	8 (4.8)	10 (6.1)
Vogt–Koyanagi–Harada	9 (2.7)	5 (3.0)	6 (3.7)
Other	21 (6.4)	2 (1.2)	7 (4.3)

- Concomitant drugs: Steroid: 89%; immunosuppressives: 37%
- Median follow-up: 74 months (IQR: 37-137 months)

## CR to anti-TNF-alpha agents

Variable		N	Odds ratio		p
<b>Disease</b>	Idiopathic	132		Reference	
	Behcet	103		2.04 (1.16, 3.60)	0.01
	Others	135		1.70 (1.02, 2.85)	0.04
<b>Gender</b>	Female	203		Reference	
	Male	167		1.51 (0.98, 2.35)	0.06
<b>Posterior uveitis</b>	0	259		Reference	
	1	111		0.65 (0.40, 1.05)	0.08
<b>Biotherapy</b>	ADA	181		Reference	
	IFX	189		0.91 (0.59, 1.42)	0.69

- Complete response (no intraocular inflammation + resolution of ME + regression of retinal vasculitis) at 6 months: 37.5%. Both drugs had similar response rates.
- BS was associated with better complete response compared to idiopathic uveitis.

## Relapse with anti-TNF-alpha agents

Variable		N	Hazard ratio	p
Disease	Idiopathic	94	Reference	
	Behcet	83	0.53 (0.33, 0.85)	0.009
	Others	99	0.61 (0.39, 0.93)	0.023
Panuveitis	0	123	Reference	
	1	153	2.07 (0.98, 4.36)	0.057
Posterior uveitis	0	185	Reference	
	1	91	2.24 (1.04, 4.82)	0.040
Biotherapy	ADA	133	Reference	
	IFX	143	0.52 (0.36, 0.77)	<0.001

- Lower risk of relapse in BS patients.
- Posterior uveitis = increased risk of relapse.
- **Lower risk of relapse with IFX (46% with ADA and 35% with IFX)**

# Infliximab for uveitis of Behçet's syndrome: a trend for earlier initiation

G. Guzelant<sup>1</sup>, D. Ucar<sup>2</sup>, S.N. Esatoglu<sup>1</sup>, G. Hatemi<sup>1</sup>, Y. Ozyazgan<sup>2</sup>, S. Yurdakul<sup>1</sup>,  
E. Seyahi<sup>1</sup>, H. Yazici<sup>1</sup>, V. Hamuryudan<sup>1</sup>

	Old group (n=43)	New Group (n=14)	p value
Mean ± SD age (years)	35 ± 8.6	37 ± 7.1	0.45
Male sex, n (%)	33 (77)	12 (86)	0.4
Median (IQR) duration of uveitis (months)	72 (45-131.5)	36.5 (11.5-86)	<b>0.043</b>
Median (IQR) duration of previous IS treatment (months)	60 (25-84)	26.5 (9-50.5)	<b>0.028</b>
Mean ± SD age at initiation of IFX treatment (years)	31 ± 8.4	33.8 ± 7.5	0.12
Median (IQR) duration of IFX treatment (months)	40 (18-50)	11.5 (8-20)	<b>&lt;0.001</b>
Patients with combined IS under IFX, n (%)	37 (86)	12 (85.7)	0.9
Previous IS treatment, n (%)			
Azathioprine	43 (100)	12 (86)	0.06
Cyclosporine-A	42 (98)	12 (86)	0.08
Interferon alpha	38 (88)	11 (79)	0.3
Cyclophosphamide*	0	1 (7)	0.07
Median (IQR) logMAR of baseline VA for R eye	0.3 (0-2)	0.7 (0.1-1.7)	0.55
Median (IQR) logMAR of baseline VA for L eye	0.22 (0.07-1)	1.2 (0.4-2)	<b>0.006</b>

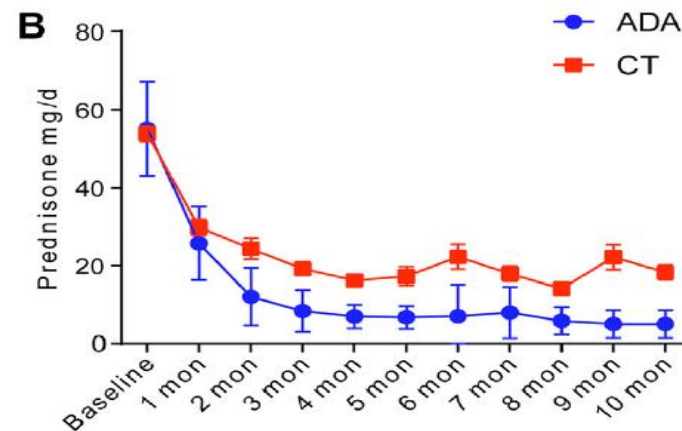
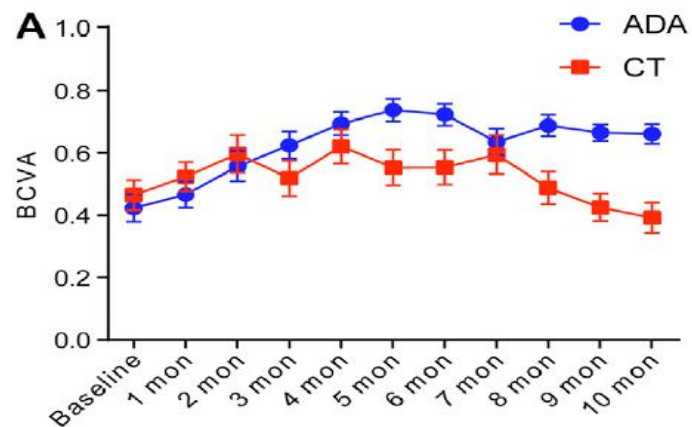
	Old group (n=43)	New Group (n=14)	p value
Patients with attacks			
before IFX, n (%)	32 (74.4)	10 (71.4)	0.8
under IFX, n (%)	23 (53.4)	1 (7)	<b>0.002</b>
Outcome of VA after IFX therapy			
improved, n (%)			
R eye	14 (32)	3 (21)	0.4
L eye	14 (32)	5 (36)	0.8
stable, n (%)			
R eye	12 (28)	9 (64)	<b>0.01</b>
L eye	21 (49)	8 (57)	0.5
worse, n (%)			
R eye	17 (40)	2 (14)	0.08
L eye	7 (16)	1 (7)	0.39

- **New group (after 2013) were given IFX earlier with better visual acuity compared to the old group (2002-2012)**
- **Less relapses and more patients with stable visual acuity in the new group**

# The Efficacy of Adalimumab as an Initial Treatment in Patients with Behçet's Retinal Vasculitis

Shizhao Yang<sup>†</sup>, Zhaohao Huang<sup>†</sup>, Yunwei Hu<sup>†</sup>, Jian Zhang, Xiuxing Liu, He Li, Lihui Xie, Feng Wen, Dan Liang\* and Wenru Su\*

- A retrospective study comparing first-line adalimumab with conventional immunosuppressives
- Better visual acuity, less frequent relapses and lower angiogram scores with adalimumab



Case series of vascular Behçet's	TNFi	Patients with a good response				Adverse events
		Pulmonary artery involvement	Non-pulmonary arteries	Vena cava thrombosis, Budd-Chiari	Intracardiac thrombosis	
Hamuryudan , 2015 <sup>1</sup>	13 IFX	9/13	-	-	-	1 aspergillosis 1 tuberculosis
Chan, 2016 <sup>2</sup>	5 IFX 2 ADA	7/7	2/2	1/1	3/3	1 recurrent pneumonia
Desbois, 2018 <sup>3</sup>	15 IFX 3 ADA	3/4	4/5	5/5	5/5	4 infections 1 heart failure
Aksoy, 2020 <sup>4</sup>	24 IFX 3 ADA	9/9	3/4	2/3 7/9 DVT	2/2	1 pneumonia 1 tuberculosis
Lu, 2020 <sup>5</sup>	16 IFX/ADA		15/16			1 infection 1 allergic reaction
Kehribar, 2020 <sup>6</sup>	18 IFX	2/2	1/2 6/6 CST and other DVT	7/7	1/1	1 pneumonia
<b>TOTAL</b>	<b>99</b>		<b>87/99 (87%)</b>			

<sup>1</sup>Semin Arthritis Rheum. 2015;45(3):369-73. Autoimmunity Rev. 2016;15:375-8. <sup>3</sup>Clinical Immunology 2018. <sup>4</sup>Int J Rheum Dis. 2020;23(2):256-261. <sup>5</sup>Chin J Intern Med, 2020,59(04): 303-308. <sup>6</sup>Kehribar et a. Vascular 2020

# IFX for vascular involvement of Behçet's syndrome

- BS patients who were started IFX for vascular involvement between 2004 and June 2021
- Primary endpoint: **Remission at month 6**
- Remission was defined as:
  - 1) Lack of new clinical signs or symptoms associated with the vascular lesion **AND**
  - 2) C-reactive protein level <10 mg/dl **AND**
  - 3) Lack of worsening of the primary vascular lesion and lack of a new vascular lesion at another site on imaging
- For venous ulcers: Total healing of the existing ulcers

	<b>Pulmonary (n=37)</b>	<b>Non- pulmonary (n=16)</b>	<b>Venous thrombosis (n=61)</b>	<b>Venous ulcer (n=13)</b>	<b>Total (n=127)</b>
<b>Remission at month 6</b>	31 (84%)	10 (63%)	50 (82%)	1 (8%)	92 (72%)
<b>Remission at month 12</b>	21 (57%)	8 (50%)	40 (66%)	2 (15%)	71 (56%)
<b>Relapse during IFX</b>	6 (16%)	7 (44%)	4 (7%)	0	17 (13%)
<b>Patients who discontinued</b>	23 (62%)	6 (37%)	31 (51%)	9 (69%)	69 (54%)
<b>Remission</b>	6	0	15	1	22 (17%)
<b>Inefficacy</b>	1	3	3	4	11 (9%)
<b>Relapse</b>	2	2	1	0	5 (4%)
<b>Adverse event</b>	4	2	7	1	14 (11%)
<b>Noncompliance</b>	4	0	3	3	10 (8%)
<b>Others</b>	8	0	2	0	10 (8%)
<b>Death</b>	2	0	2	0	4 (3%)




# Adverse events leading to IFX discontinuation (n=14)

- Infusion reactions (n=5)
- Tuberculosis (n=1)
- Disseminated zona (n=1)
- Aortic graft infection (n=1)
- Lung adenocarcinoma (n=1)
- Fibromyxoid sarcoma (n=1)
- Heart failure (n=1)
- Systemic lupus erythematosus (n=1)
- Palmoplantar pustulosis (n=1)
- Auricular chondritis (n=1)

## Reasons for death (n=4)

- Pulmonary hypertension related right heart failure due to pulmonary artery thrombosis (n=2)
- Lung adenocarcinoma (n=1)
- Sepsis (n=1)

## Emergence of new manifestations during infliximab treatment in Behçet's syndrome

Nur Beyza Tukek<sup>1</sup>, Sinem Nihal Esatoglu<sup>2</sup>, Gulen Hatemi <sup>2</sup>,  
Elif Buse Caliskan<sup>1</sup>, Yilmaz Ozyazgan<sup>3</sup>, Didar Ucar<sup>3</sup>, Yesim Ozguler<sup>2</sup>,  
Emire Seyahi<sup>2</sup>, Melike Melikoglu<sup>2</sup>, Ugur Uygunoglu<sup>4</sup>, Aksel Siva<sup>4</sup>,  
Zekayi Kutlubay<sup>5</sup>, Ibrahim Hatemi<sup>6</sup>, Aykut Ferhat Celik<sup>6</sup>, Serdal Ugurlu <sup>2</sup>,  
Izzet Fresko<sup>2</sup>, Sebahattin Yurdakul<sup>2</sup>, Hasan Yazici<sup>2</sup> and  
Vedat Hamuryudan <sup>2</sup>

- The patient charts of all BS patients who received IFX between 2004 and 2020 were reviewed.
- Those who developed new manifestations were identified.
- Definition of 'new manifestation':
  - Any manifestation that developed for the first time during IFX treatment (within 12 weeks after the last infusion)
  - A vascular lesion that emerged at a different vessel site

282 BS patients were treated with IFX  
between 2004 and June 2021

**Uveitis  
n=137**

**Vascular  
involvement  
n=91**

**Nervous  
system  
involvement  
n=40**

**Gastrointestinal  
involvement  
n=10**

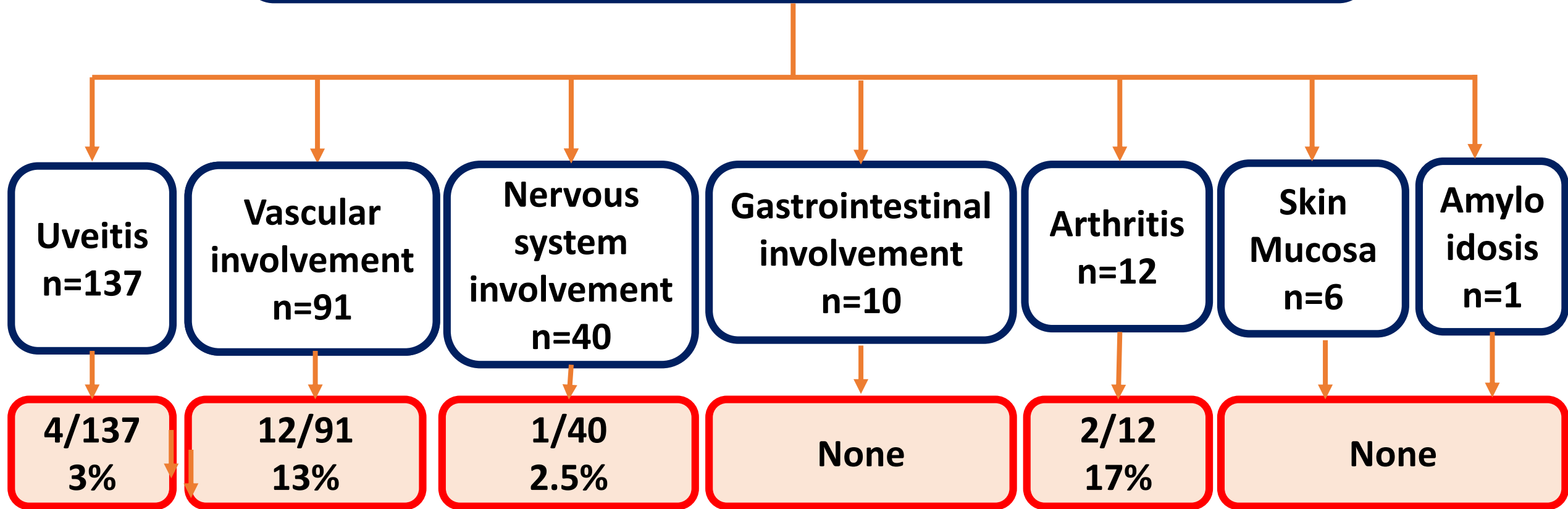
**Arthritis  
n=12**

**Skin  
Mucosa  
n=6**

**Amylo  
idosis  
n=1**

- Fifteen patients had more than one involvement requiring IFX

282 BS patients were treated with IFX  
between 2004 and June 2021

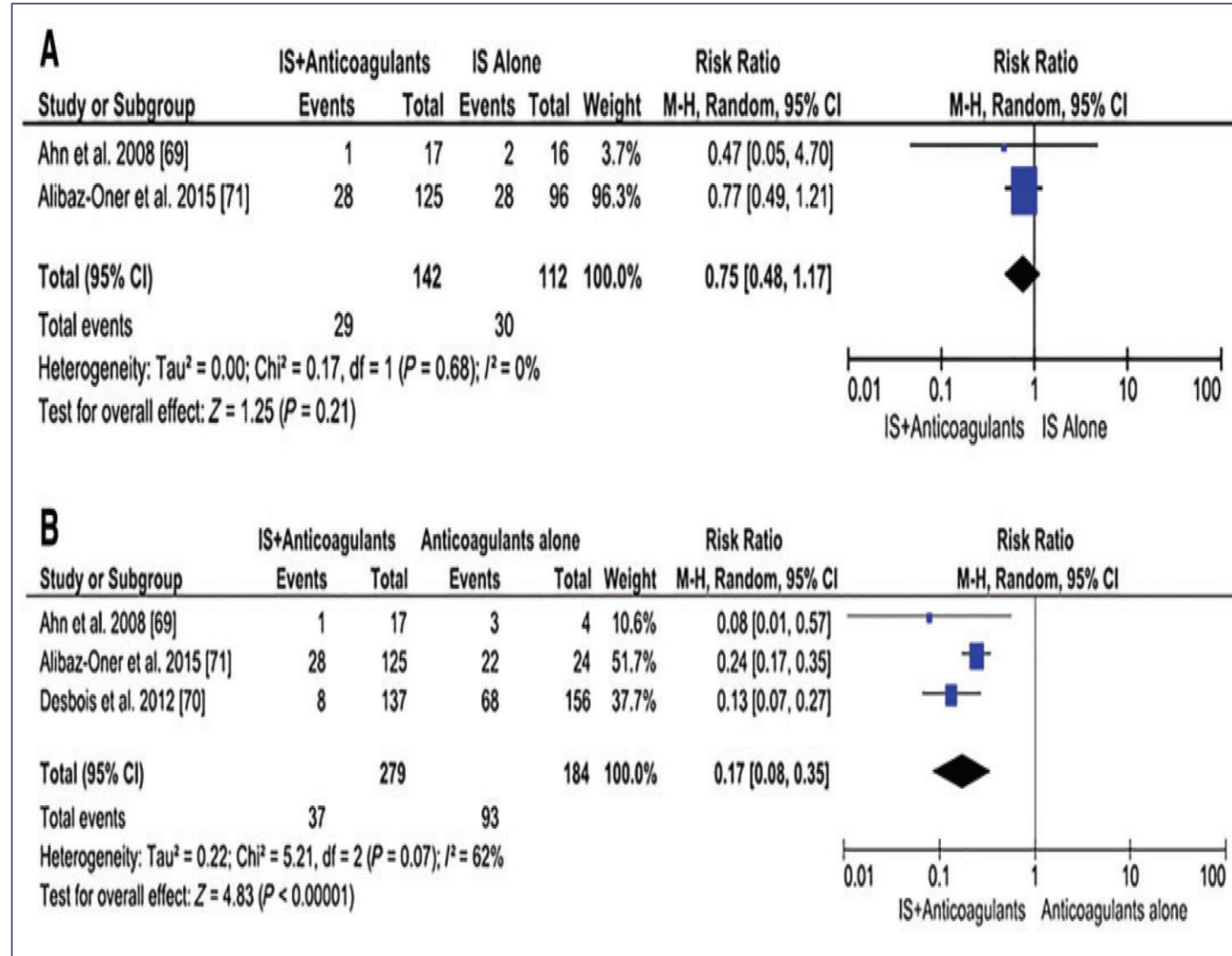


**19 (7%)** patients developed a total of **23** new manifestations during a mean follow-up of 30 (IQR: 13-52) months.

New manifestations	n (%)	Main reason for starting IFX
<b>Vascular involvement</b>	11 (48 %)	
Pulmonary artery thrombosis	2	Vascular
Pulmonary artery aneurysm	1	Uveitis
Coronary artery involvement	2	Vascular
Deep vein thrombosis	1	Neuro-BS
Superficial thrombophlebitis	5	2 uveitis, 1 arthritis, 1 vascular, 1 venous ulcer
<b>Arthritis</b>	5 (22 %)	4 vascular, 1 venous ulcer
<b>Erythema nodosum</b>	3 (13 %)	1 uveitis, 1 vascular, 1 neuro-BS
<b>Gastrointestinal involvement</b>	3 (13 %)	1 uveitis, 1 vascular, 1 arthritis
<b>Nervous system involvement</b>	1	Vascular

# Should we anticoagulate Behçet's syndrome patients with thrombosis?

- Pulmonary embolism is rare
- Does not decrease relapse risk
- Bleeding risk during anticoagulation:
  - Desbois (2012) - %2,4
  - Alibaz-Öner (2015) - %3
- If you decide to anticoagulate
  - Screen for arterial aneurysms



Alibaz-Oner et al. Medicine (Baltimore) (2015)

Desbois et al. Arthritis Rheum 2012

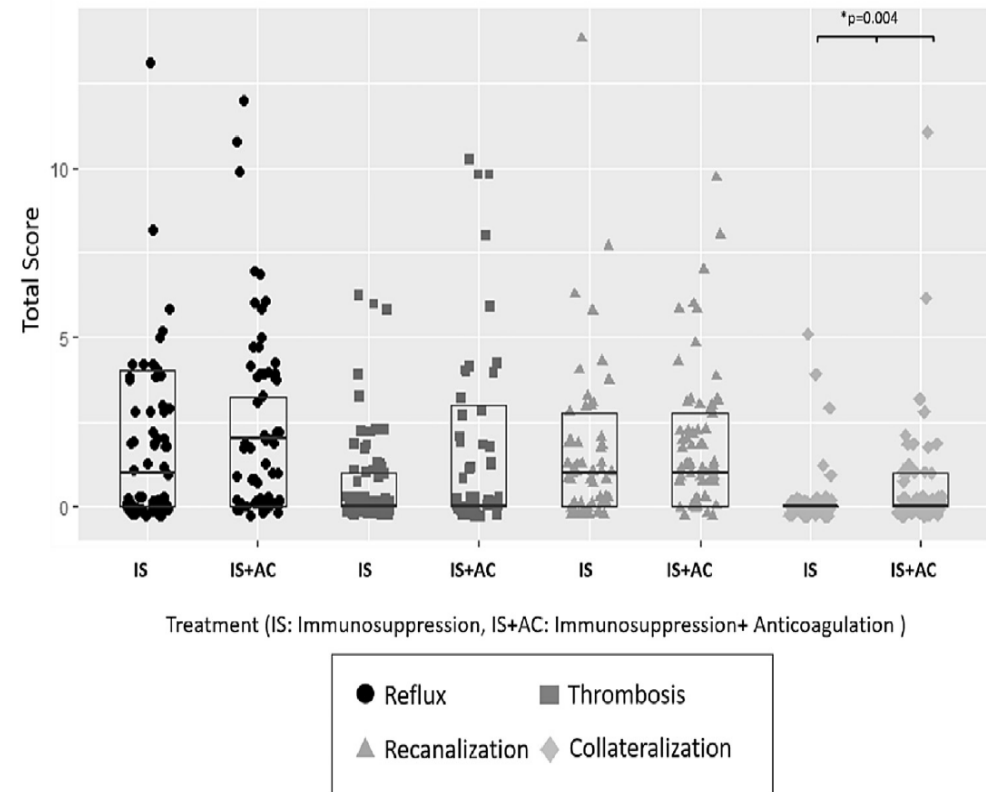
Taşcılar et al. Rheumatolo (Oxford) 2014

Özgüler et al. Systematic review for updating EULAR recommendations; Rheumatology 2018 Aug

# Predictors for the risk and severity of post-thrombotic syndrome in vascular Behçet's disease

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- 205 Behçet's patients with DVT
  - 62% PTS, 18% severe PTS
- 26% had recurrences
- Treatment (at least 3 months):
  - 11 – no treatment
  - 77 (39%) only immunosuppressives
  - 23 (12%) only anticoagulants
  - 85 (43%) both



# Factors associated with PTS and severe PTS

Immunosuppressive use was associated with less frequent severe PTS – anticoagulation was not associated

**Table II.** Multivariate analysis of presence of PTS

Variable	OR (95% CI)	P value
Current age	1.05 (1.01-1.10)	.048
BSAS	1.06 (1.04-1.10)	.000
Bilateral Doppler US involvement	2.81 (1.18-6.67)	.019
Iliofemoral residual thrombi	2.74 (1.02-7.38)	.045

BSAS, Behçet Syndrome Activity Score; CI, confidence interval; OR, odds ratio; PTS, post-thrombotic syndrome; US, ultrasound.

**Table III.** Multivariate analysis of presence of moderate to severe PTS

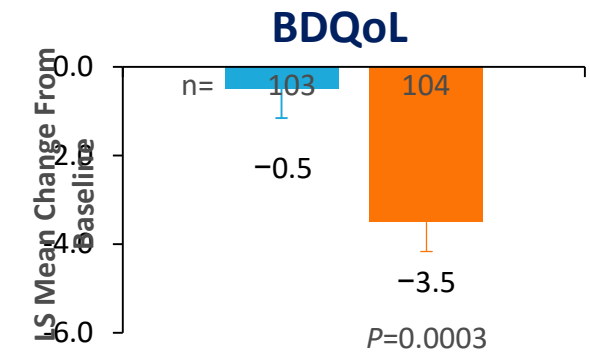
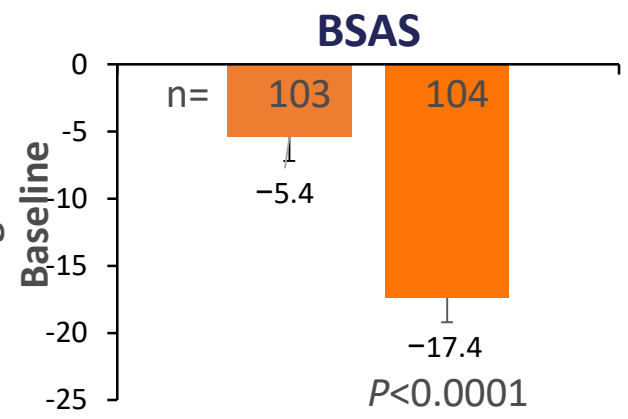
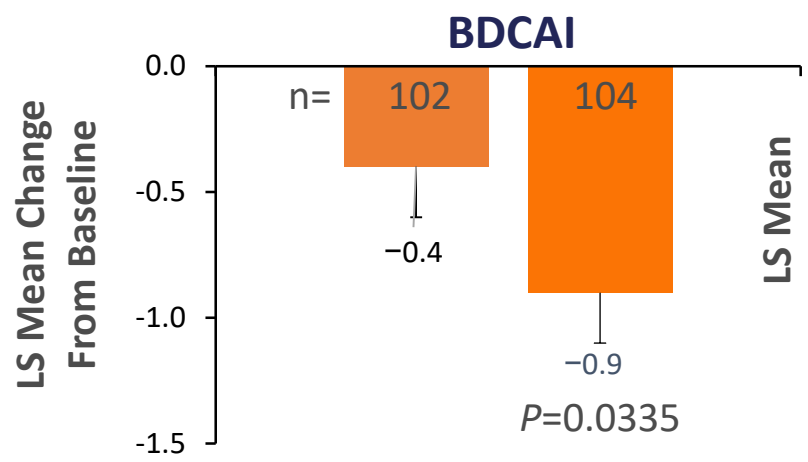
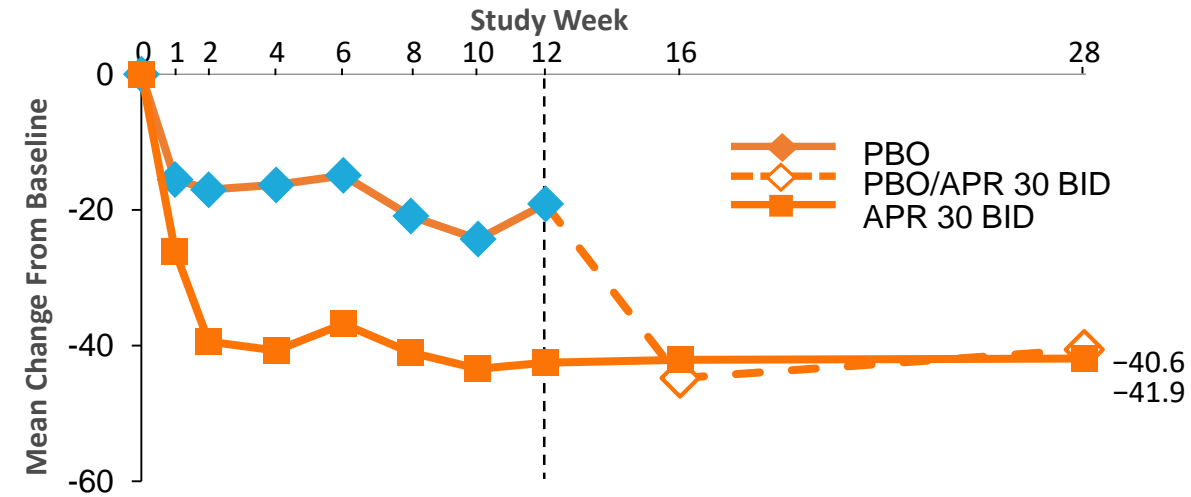
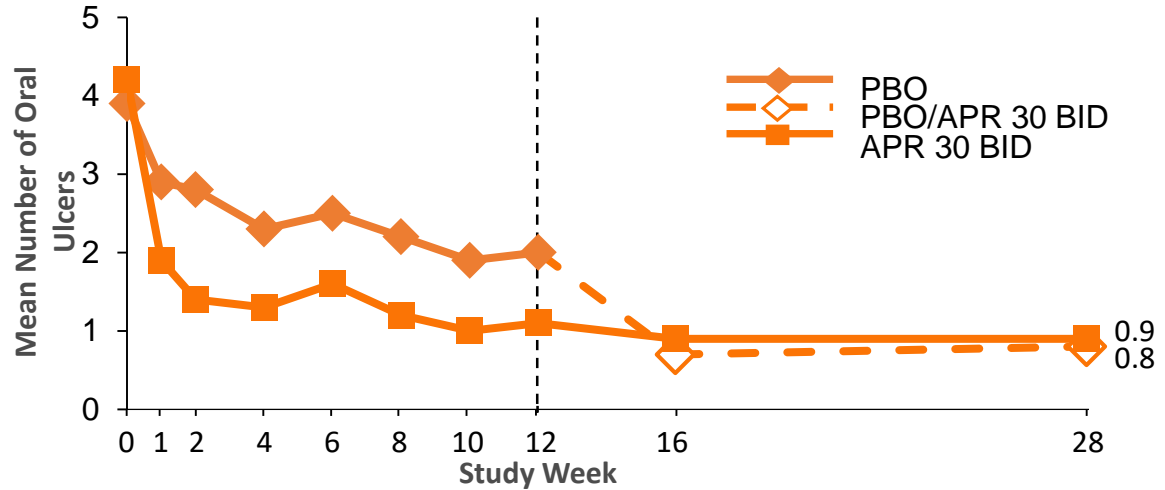
Variable	OR (95% CI)	P value
BMI	1.09 (1.001-1.19)	.048
Immunosuppressive use	0.10 (0.02-0.05)	.005

BMI, Body mass index; CI, confidence interval; IS, immunosuppressive; OR, odds ratio; PTS, post-thrombotic syndrome.

# Trial of Apremilast for Oral Ulcers in Behçet's Syndrome

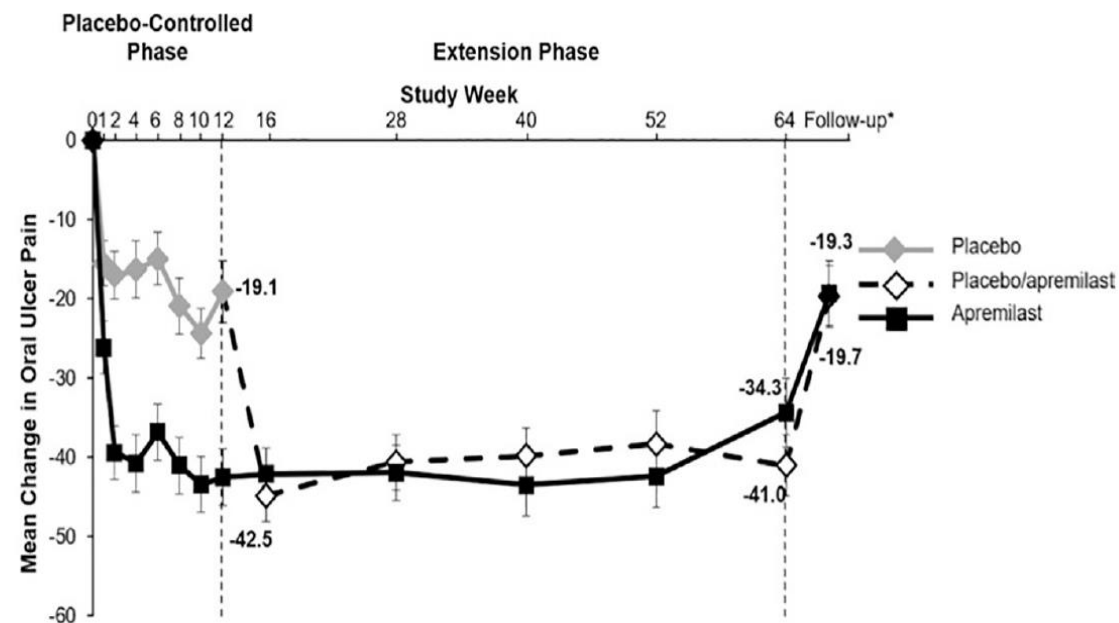
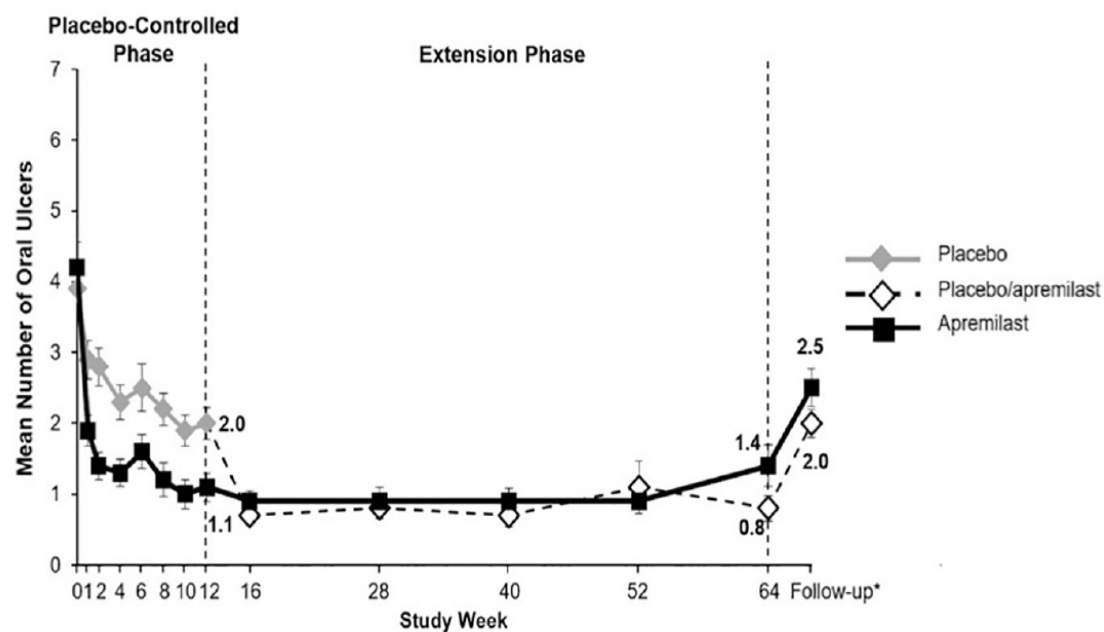
Gülen Hatemi, M.D., Alfred Mahr, M.D., M.P.H., Ph.D., Yoshiaki Ishigatsubo, M.D., Ph.D., Yeong-Wook Song, M.D., Mitsuhiro Takeno, M.D., Ph.D., Doyoung Kim, M.D., Ph.D., Melike Melikoğlu, M.D., Sue Cheng, M.D., Ph.D., Shannon McCue, Ph.D., Maria Paris, M.D., Mindy Chen, M.S., and Yusuf Yazici, M.D.

- Number of oral ulcers
- Pain of oral ulcers
- Overall disease activity
- Quality of life



# Apremilast for oral ulcers associated with active Behçet's syndrome over 68 weeks: long-term results from a phase 3 randomised clinical trial

G. Hatemi<sup>1</sup>, A. Mahr<sup>2</sup>, M. Takeno<sup>3</sup>, D.Y. Kim<sup>4</sup>, D. Saadoun<sup>5</sup>, H. Direskeneli<sup>6</sup>, M. Melikoğlu<sup>1</sup>, S. Cheng<sup>7</sup>, S. McCue<sup>7</sup>, M. Paris<sup>7</sup>, M. Chen<sup>7</sup>, Y. Yazici<sup>8</sup>

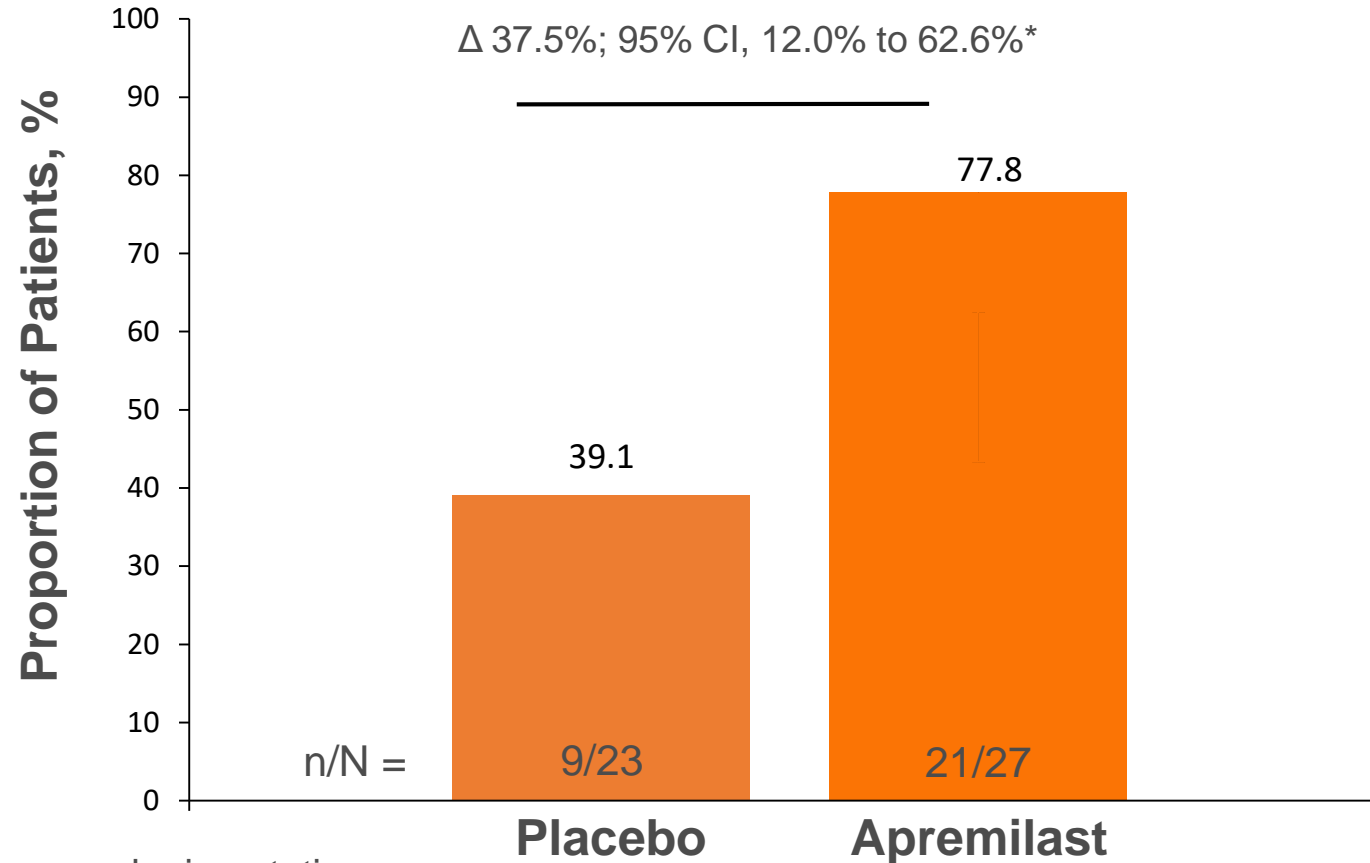


Improvement in the number of oral ulcers was sustained in patients continuing APR 30 mg BID for up to 64 weeks and emerged in patients who switched from PBO to APR at Week 12 through Week 64

# POOLED ANALYSIS: GREATER PROPORTION OF GENITAL ULCERS COMPLETE RESPONSE AT WEEK 12 WITH APREMILAST

RELIEF &  
Phase II Study

## Patients With Genital Ulcers at Baseline

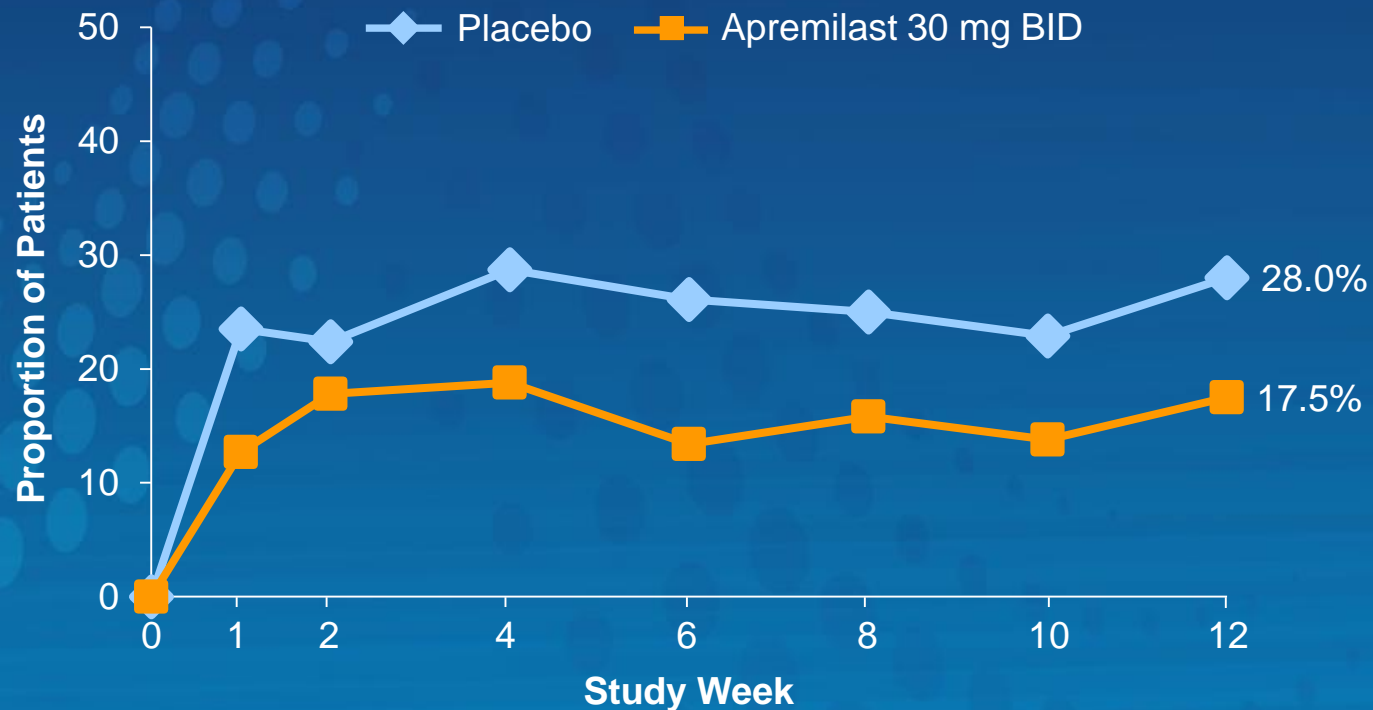


ITT population; non-responder imputation.

\* $P = 0.011$ , apremilast 30 mg BID vs placebo. Patients with genital ulcers at baseline in the phase II study: apremilast: n/N = 10/55; placebo: n/N = 6/56.

# PATIENTS WITH $\geq 1$ NEW, RECURRENT, WORSENING SKIN LESION

## OVERALL POPULATION

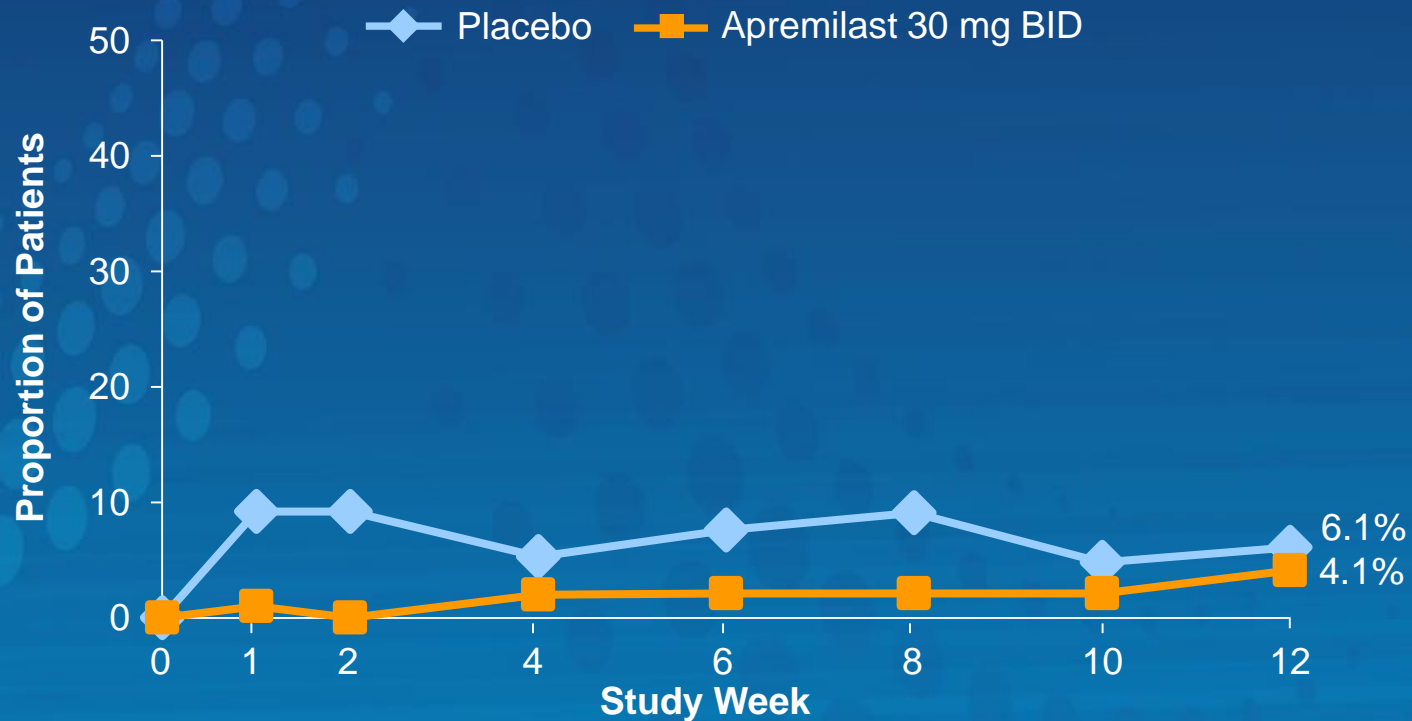


Weeks	1	2	4	6	8	10	12
PBO, n	98	98	94	92	88	83	82
APR, n	102	101	101	97	95	94	97

ITT population. Data as observed. n = number of patients.

# PATIENTS WITH $\geq 1$ NEW, RECURRENT, WORSENING ARTHRITIS

## OVERALL POPULATION



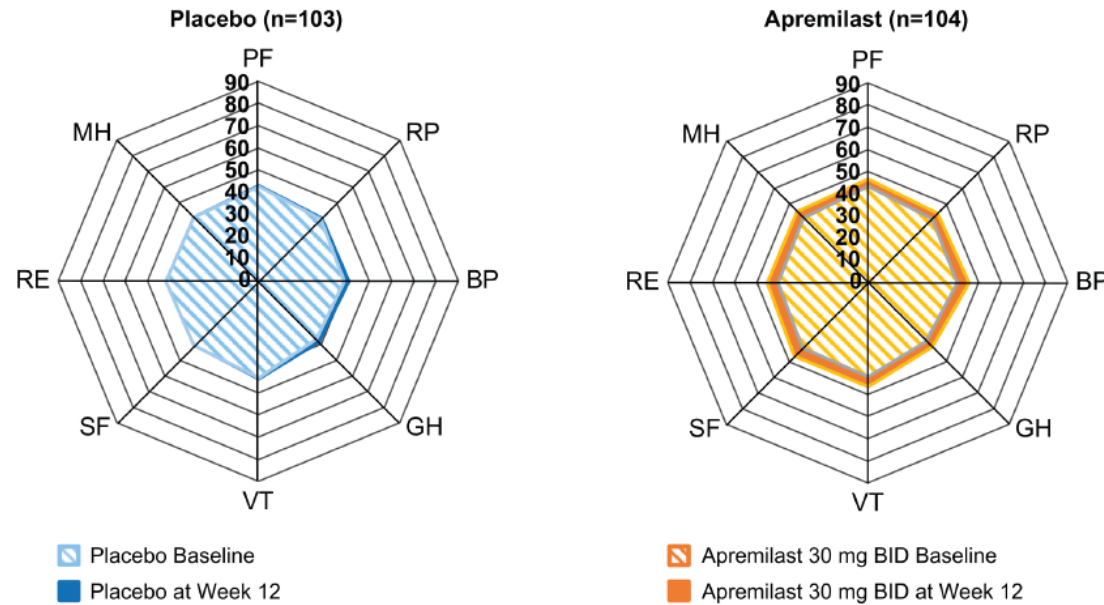
Weeks	1	2	4	6	8	10	12
PBO, n	98	98	94	92	88	83	82
APR, n	102	101	101	97	95	94	97

ITT population. Data as observed. n = number of patients.

# Impact of Apremilast on quality of life in Behçet's syndrome: analysis of the phase 3 RELIEF study

A

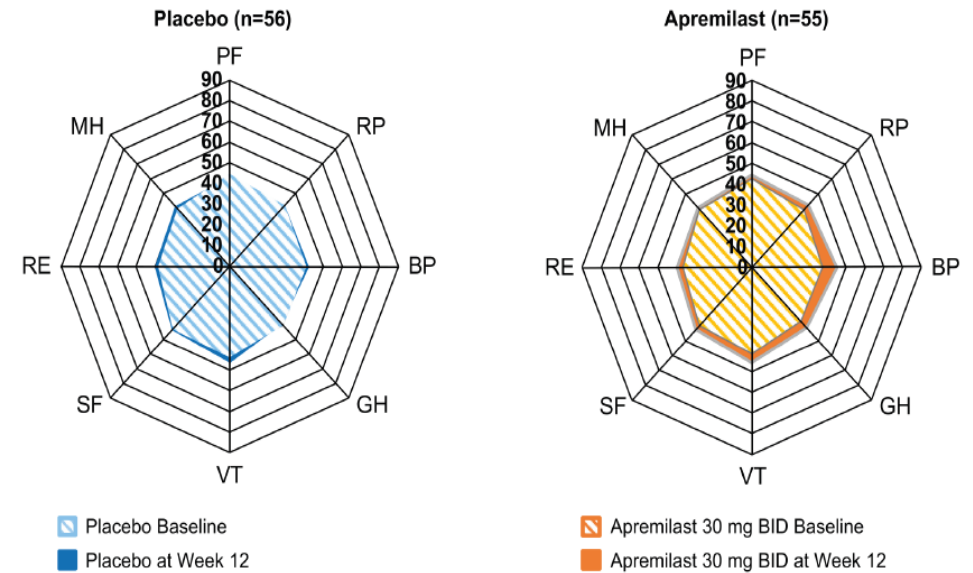
RELIEF



	Placebo		Apremilast	
	Baseline	Week 12	Baseline	Week 12
PF	42.6	43.1	43.4	46.5
RP	39.7	40.2	40.9	44.3
BP	38.8	40.8	40.3	45.7
GH	36.7	38.5	37.1	40.7
VT	43.3	43.9	42.2	46.9
SF	41.0	40.8	41.6	46.8
RE	41.6	40.8	40.4	45.5
MH	41.0	40.9	41.2	45.1

B

Phase 2 Study



	Placebo		Apremilast	
	Baseline	Week 12	Baseline	Week 12
PF	44.5	42.3	42.5	44.4
RP	41.6	40.9	39.1	42.3
BP	40.8	41.4	37.4	45.2
GH	40.3	38.7	36.7	41.1
VT	44.0	45.6	41.6	45.6
SF	43.0	42.7	39.4	42.3
RE	78.4	81.2	74.7	82.3
MH	39.7	40.2	39.4	40.4

# Impact of apremilast on quality of life in Behçet's syndrome: analysis of the phase 3 RELIEF study

**Table 1** Correlation of change from baseline in SF-36v2 PCS, PF and MCS and BDQoL with Behçet's Disease Activity, Week 12 (modified intent-to-treat population, LOCF)

Change from baseline at week 12	Apremilast 30 mg two times per day n=104			
	PCS	PF	MCS	BDQoL
OU count*	-0.11 p=0.2472	-0.07 p=0.4734	-0.02 p=0.8746	0.07 p=0.4656
Pain VAS	-0.28 p=0.0035	-0.10 p=0.3072	-0.09 p=0.3875	0.28 p=0.0036
BSAS	-0.38 p<0.0001	-0.20 p=0.0435	-0.16 p=0.0954	0.22 p=0.0237
BDCAF†				
BDCAI	-0.19 p=0.0505	0.01 p=0.9108	-0.06 p=0.5380	0.04 p=0.6680
Physician's perception	-0.10 p=0.3206	0.01 p=0.9021	-0.13 p=0.1734	0.20 p=0.0465
Patient's perception	-0.27 p=0.0060	-0.13 p=0.2031	-0.08 p=0.4283	0.23 p=0.0194
BDQoL	-0.18 p=0.0606	-0.13 p=0.1884	-0.45 p<0.0001	-

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