

Síndrome de hiper-IgD y fiebre periódica Resultados del ensayo clínico sore eficacia y seguridad de canakinumab

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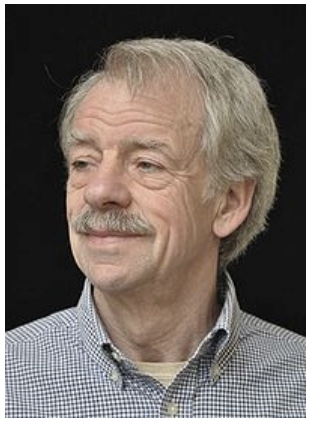
Research grants
Honorarium for lectures
Clinical trial participation

Síndrome de hiper-IgD

Canakinumab en síndrome de hiper-IgD

Síndrome de hiper-IgD

Ensayo canakinumab en HIDS



Jos WM van der Meer

The Lancet · Saturday 19 May 1984

HYPERIMMUNOGLOBULINAEMIA D AND PERIODIC FEVER: A NEW SYNDROME

JOS W. M. VAN DER MEER JAAK M. VOSSEN
JIRI RADL JANNY A. VAN NIEUWKOOP
GHRIS J. L. M. MEYER* SACHA LOBATTO
RALPH VAN FURTH

Fiebre Mediterránea Familiar



TRAPS

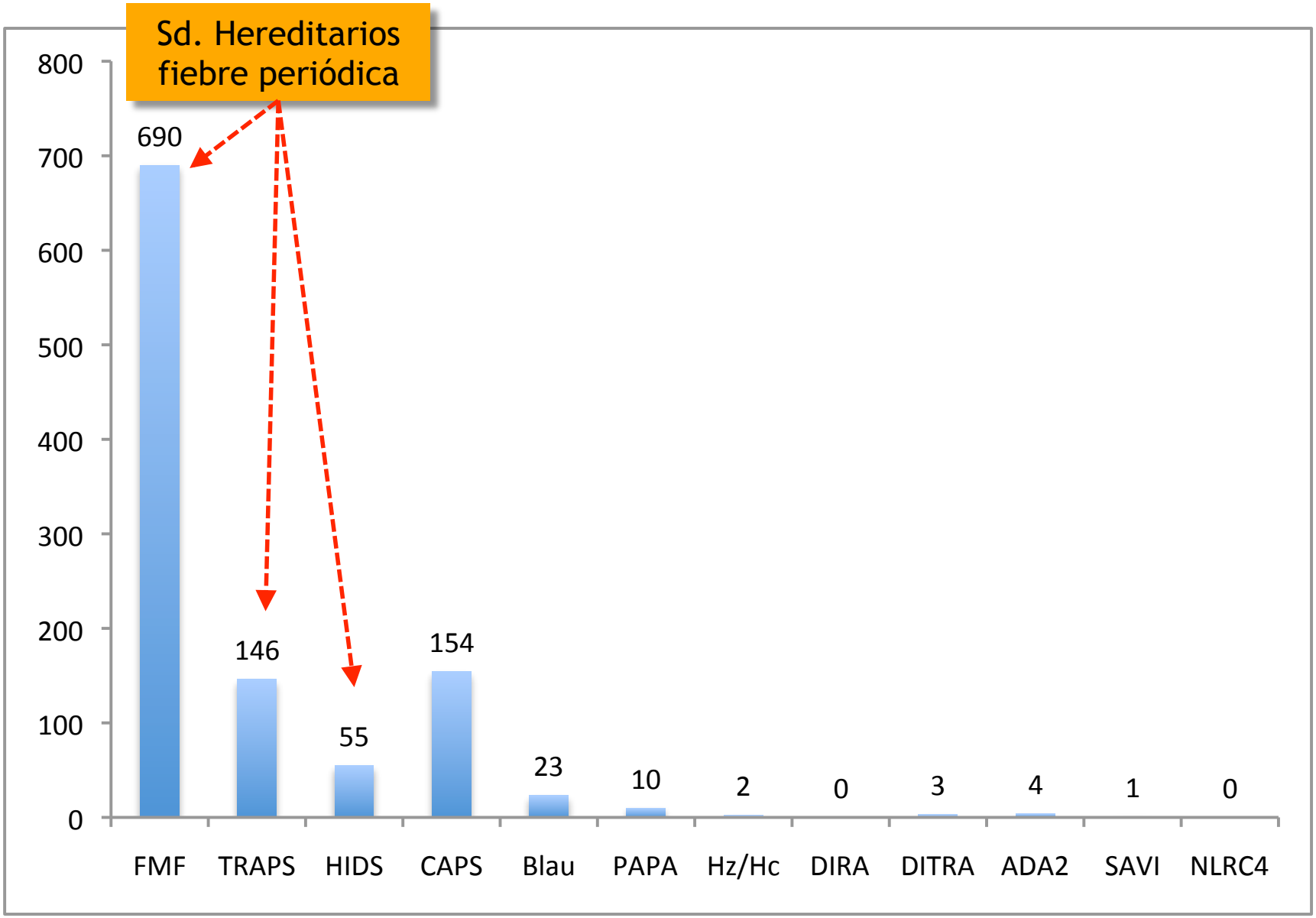
Quarterly Journal of Medicine, New Series LI, No. 204, pp. 469–480, Autumn 1982

Familial Hibernian Fever

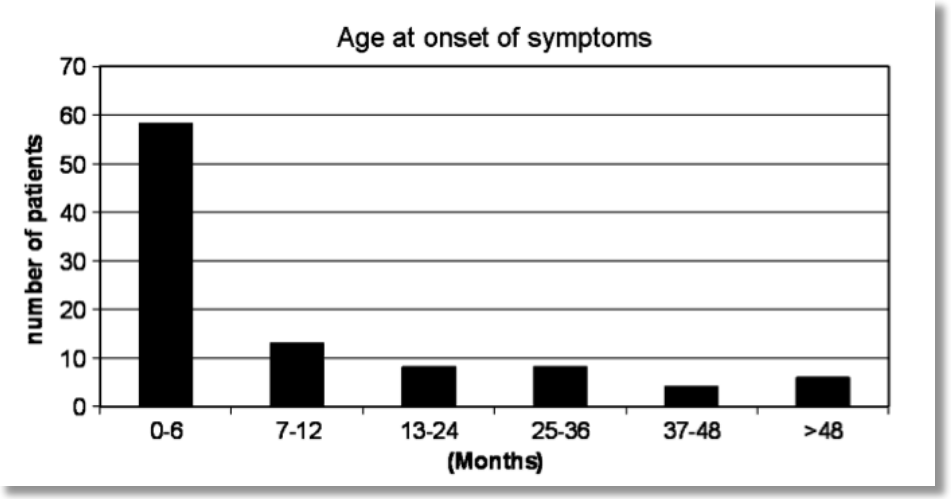
L. M. WILLIAMSON*, D. HULL†, R. MEHTA§
W. G. REEVES‡, B. H. B. ROBINSON§, AND P.

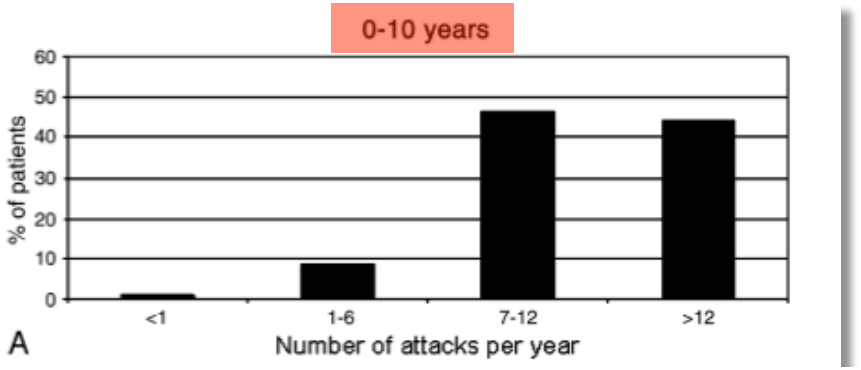


Ensayo canakinumab en HIDS



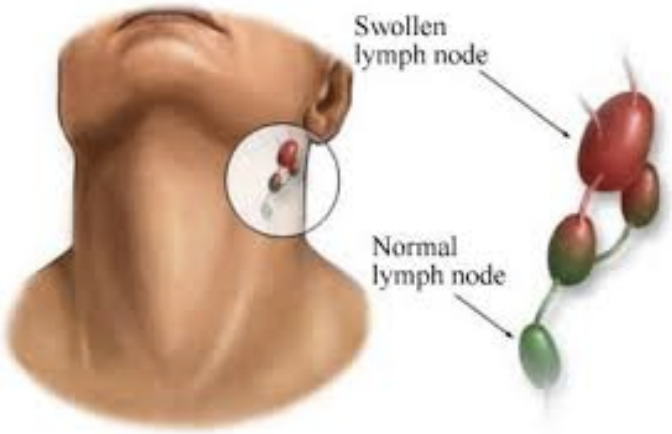
Ensayo canakinumab en HIDS





Medicine 2008; 87: 301

Ensayo canakinumab en HIDS



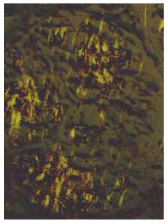










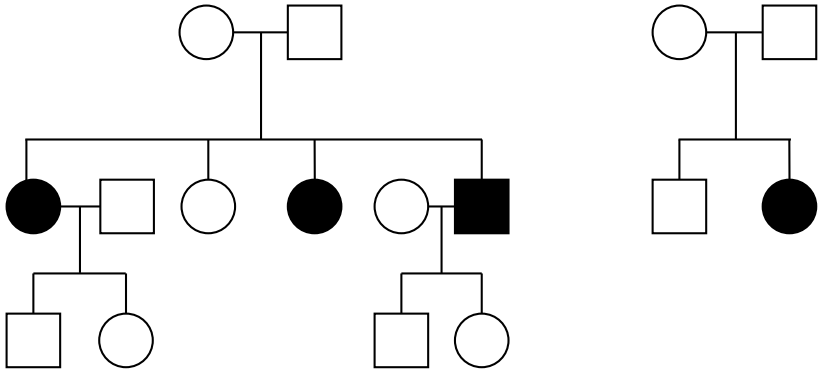


Incorrect Diagnoses Made Before HIDS Diagnosis

Diagnosis	No. of Patients
FMF	13
Adult-onset Still disease	6
JCA	5
Rheumatic fever	3
Chronic infection	3
Behçet disease	3

Medicine 2008; 87: 301

Herencia autosómica recesiva





Mutations in *MVK*, encoding mevalonate kinase, cause hyperimmunoglobulinaemia D and periodic fever syndrome

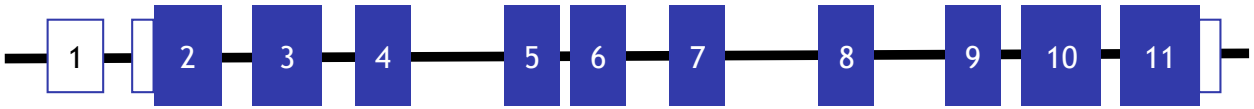
Nature Genetics 1999; 22: 175-177

Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome

Nature Genetics 1999; 22: 178-181

Ensayo canakinumab en HIDS

Gen *MVK*



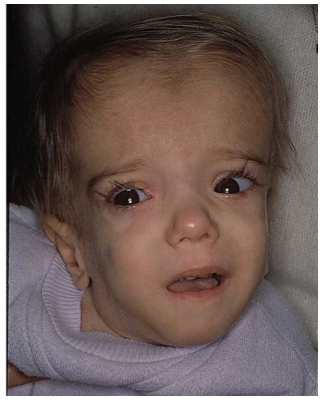
Allele Frequencies of MVK Mutations

Mutation	Allele Frequency (%)
V377I	50
I268T	14.7
H20P/N	4.4
P167L	2.4
H380R	1.5
R215Q	1.5
W188X	1.5
25 Other	All <1

Medicine 2008; 87: 301

Mevalonic Aciduria — An Inborn Error of Cholesterol and Nonsterol Isoprene Biosynthesis

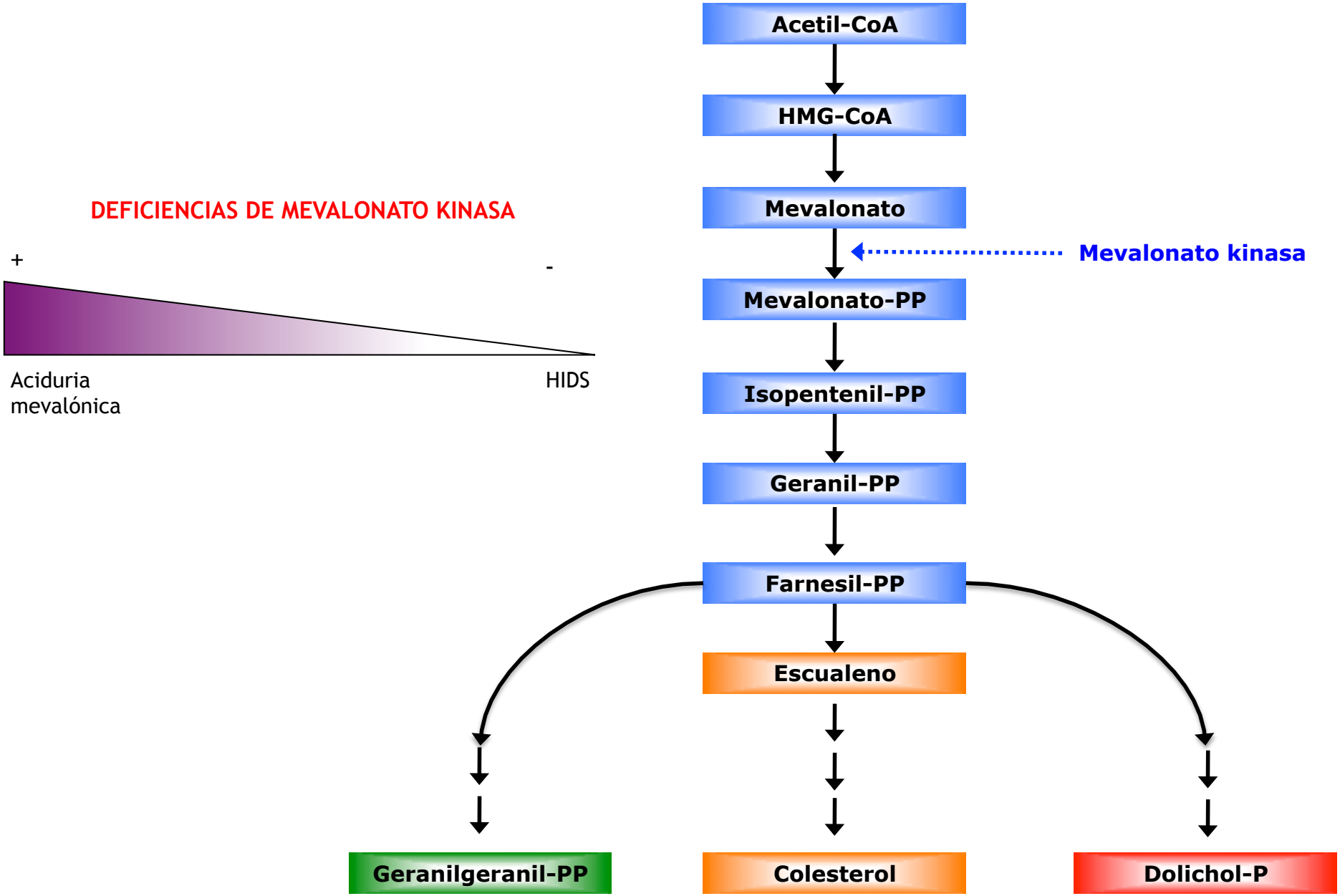
N Engl J Med 1986; 314: 1610-4

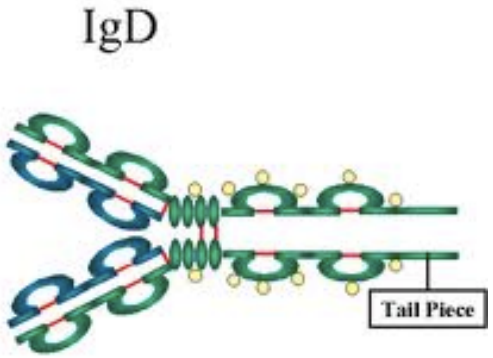


Episodios febriles recurrentes
Fiebre
Adenopatías cervicales bilaterales
Dolor abdominal
hepatoesplenomegalia

Debut temprano
Fallo de medro
Dismorfia facial
Manifestaciones neurológicas graves
Cataratas

Ensayo canakinumab en HIDS





Pacientes con mutaciones en los dos alelos del gen MVK

20% valores normales

Normal en edad pediátrica / Aumento con la edad

Hiper IgD en otras enfermedades inflamatorias activas, incluyendo otras autoinflamatorias

Mal parámetro de screening de síndrome HIDS

Diagnóstico definitivo MKD

- *Genético*
- *Metabólico*
  - *Excreción urinaria de ácido mevalónico*
    - *HIDS: sutil / episodios agudos*
    - *AM: muy elevada /permanente*
  - *Actividad enzimática residual*

TABLE 5. Medications Tried and Response to Therapy in HIDS Patients*

	No Response (n)	Some Response (n)	Good Response (n)
Prednisone (n = 45)	17	17	11
Colchicine (n = 44)	37	7	0
Statin (n = 18)	12	4	2
Antibiotics (n = 13)	11	2	0
Etanercept (n = 13)	4	5	4
Anakinra (n = 11)	4	3	4
Thalidomide (n = 8)	7	1	0
Cyclosporine (n = 7)	6	1	0

*Patients may have used multiple medications.

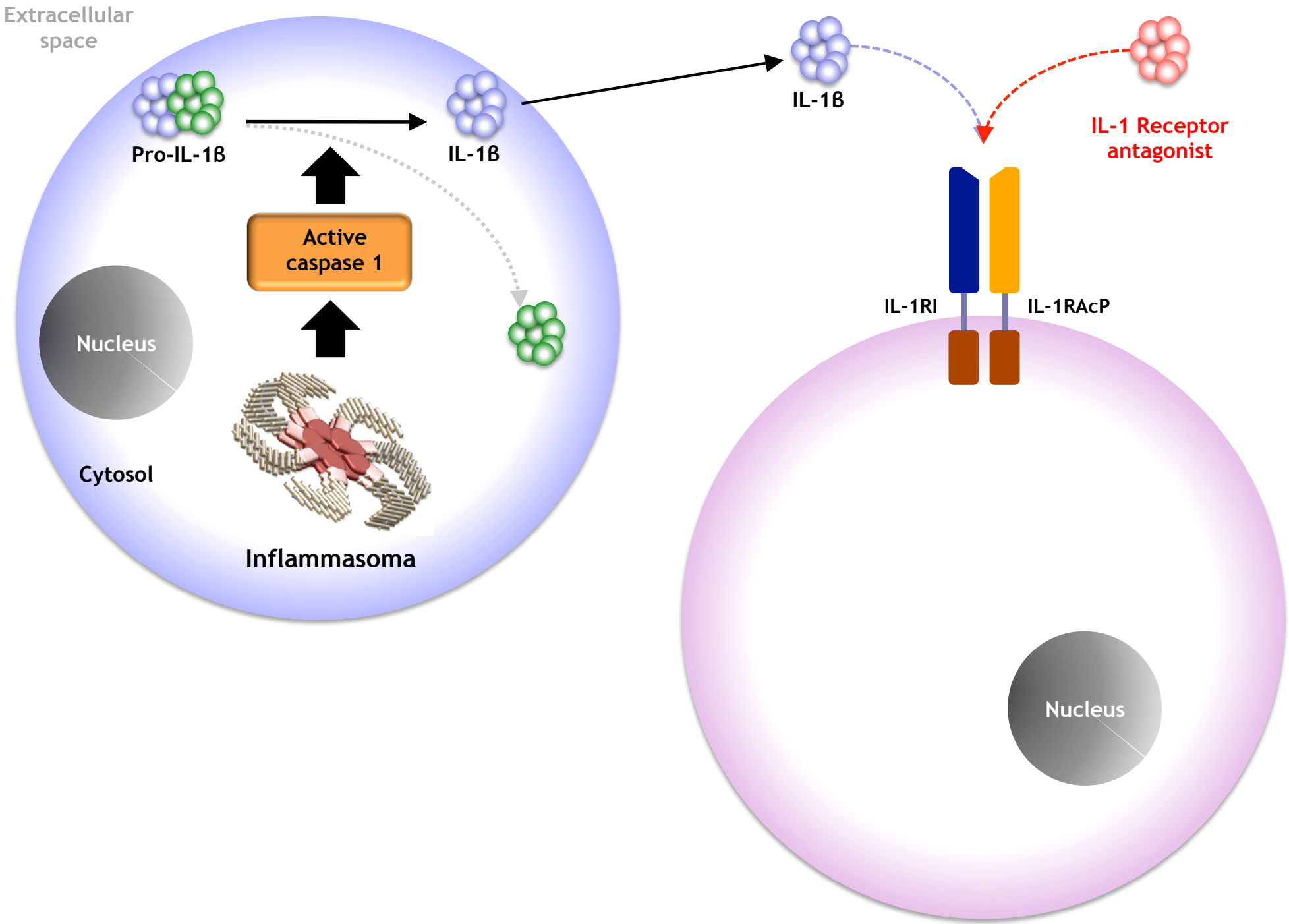
Medicine 2008; 87: 301

Síndrome de hiper-IgD

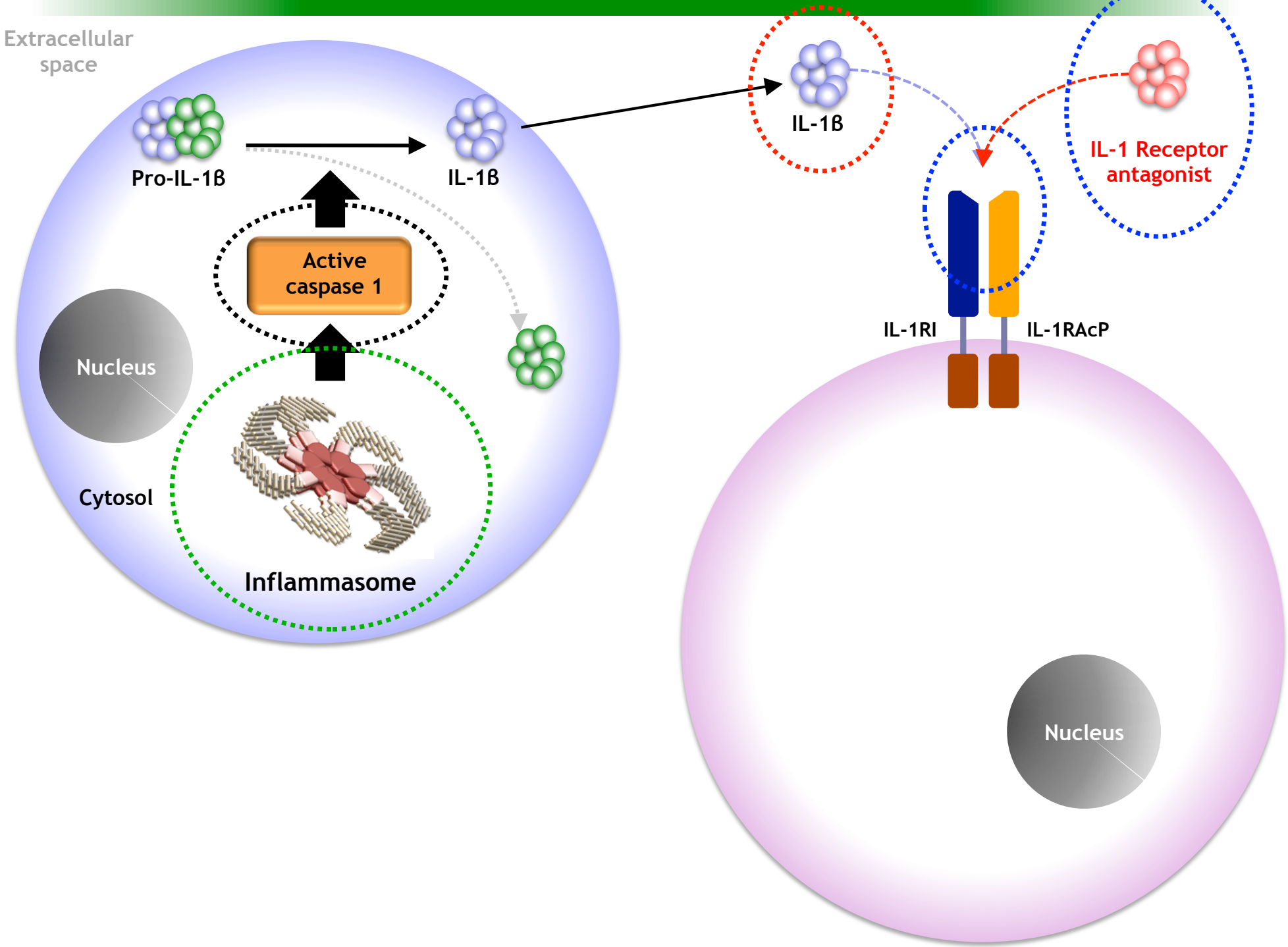
Canakinumab en síndrome de hiper-IgD

IL-1 y canakinumab

Ensayo canakinumab en HIDS



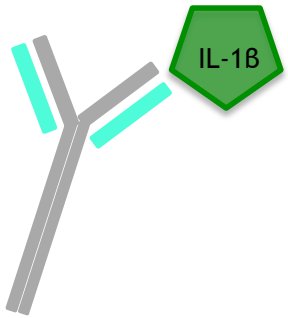
Ensayo canakinumab en HIDS



Ilaris™
Canakinumab

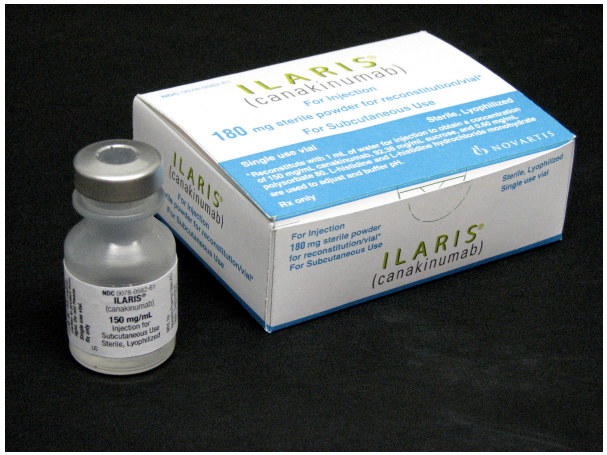
Use of Canakinumab in the Cryopyrin-Associated Periodic Syndrome

N Engl J Med 2009; 360: 2416-25

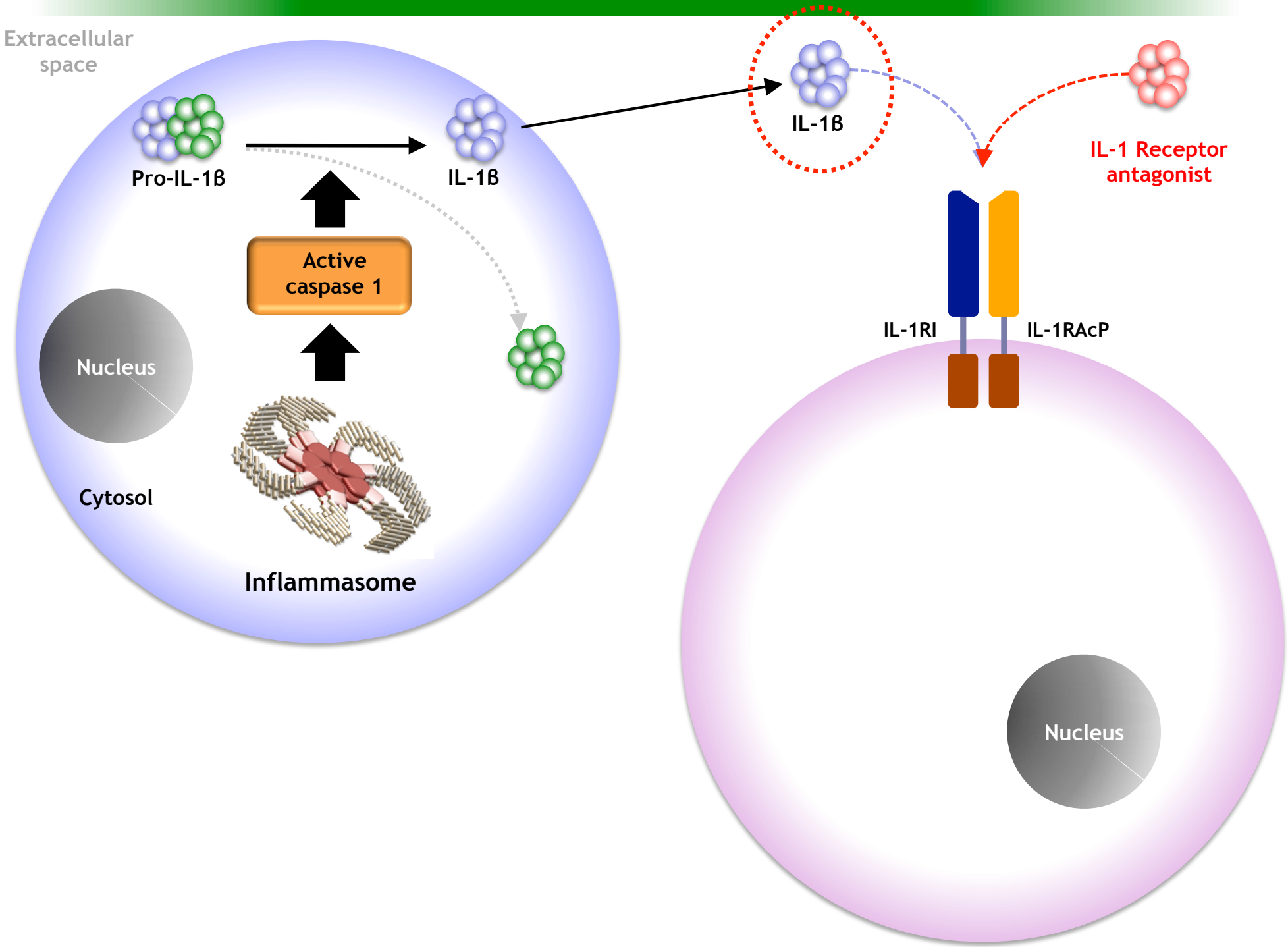


Two-year results from an open-label, multicentre, phase III study evaluating the safety and efficacy of canakinumab in patients with cryopyrin-associated periodic syndrome across different severity phenotypes

Ann Rheum Dis 2011; 70: 2095-102



Ensayo canakinumab en HIDS



Síndrome de hiper-IgD

Canakinumab en síndrome de hiper-IgD

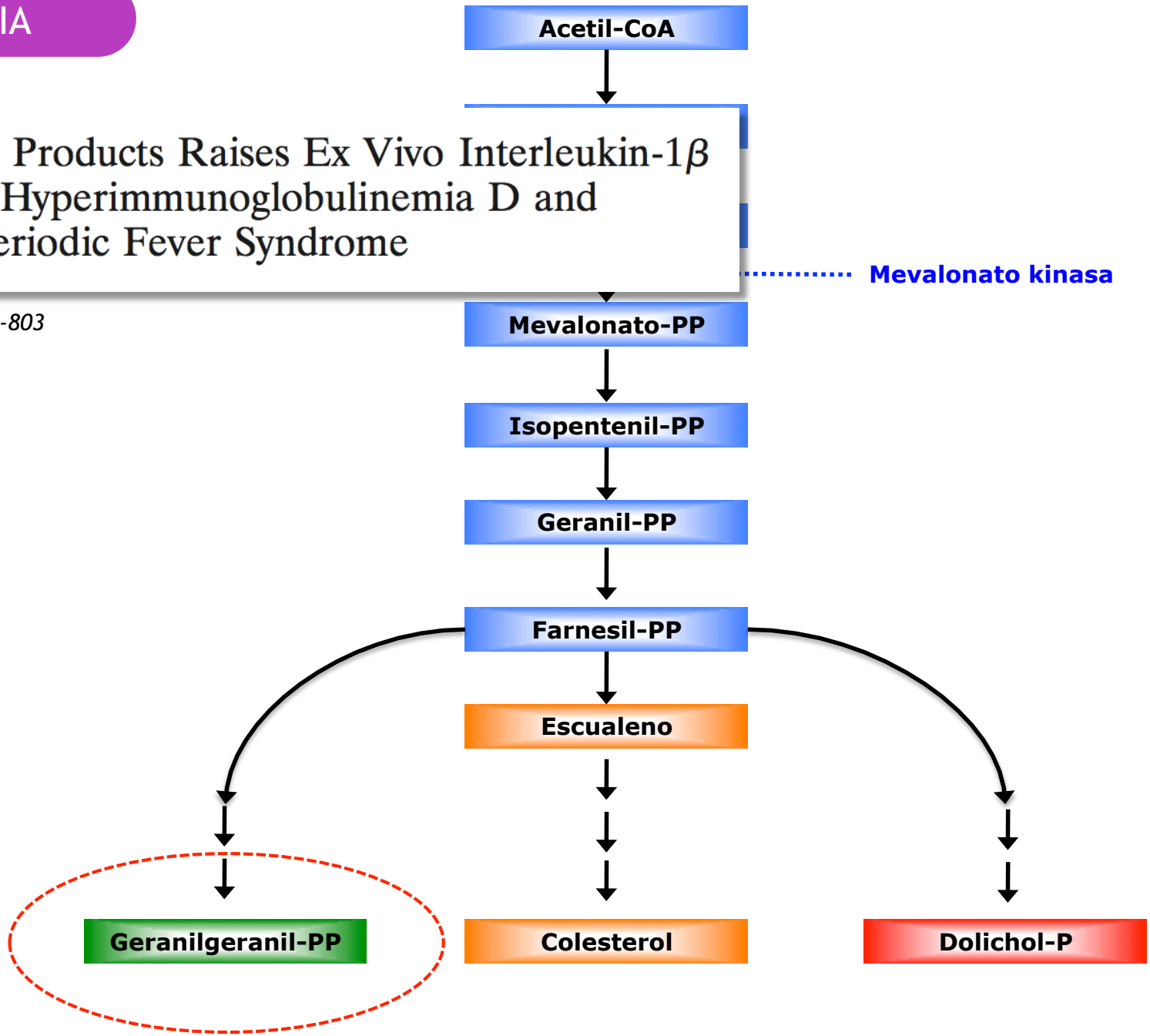
IL-1 y canakinumab

Base racional del ensayo clínico

FISIOPATOLOGIA

Lack of Isoprenoid Products Raises Ex Vivo Interleukin-1β Secretion in Hyperimmunoglobulinemia D and Periodic Fever Syndrome

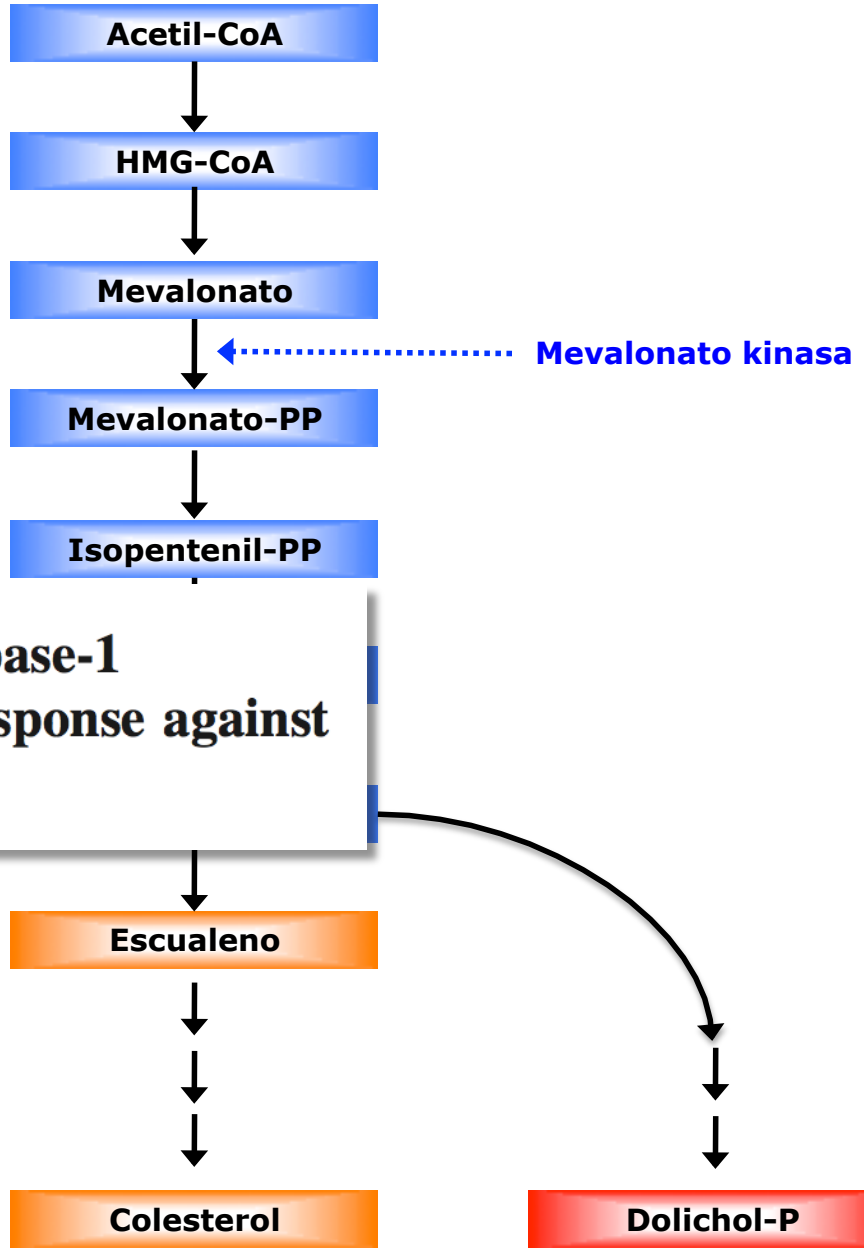
Arthritis Rheum 2002; 46: 2794-803



FISIOPATOLOGIA



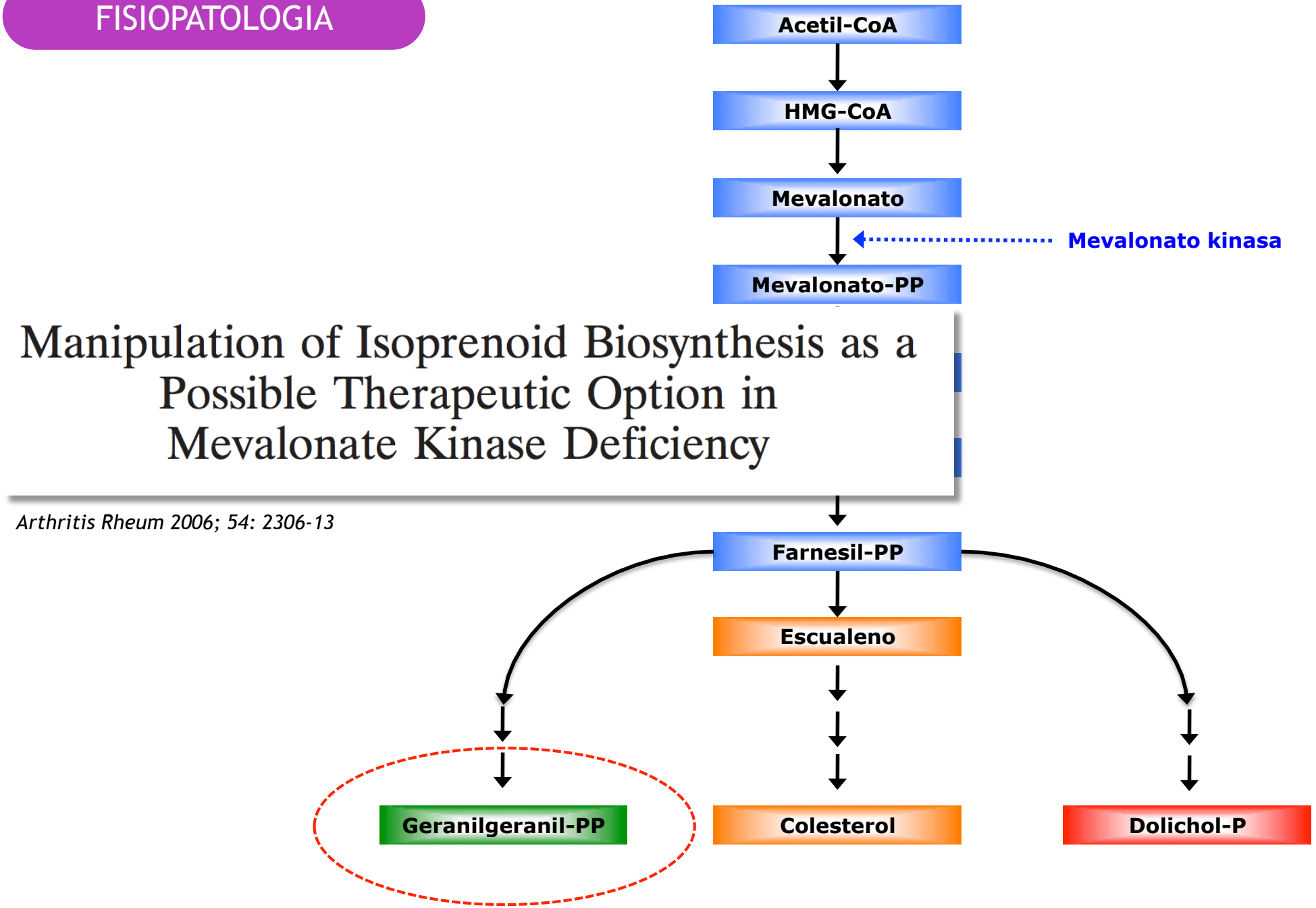
Inflammasome



Geranylgeraniol Regulates Negatively Caspase-1 Autoprocessing: Implication in the Th1 Response against *Mycobacterium tuberculosis*[1]

J Immunol 2004; 173: 4936-44

FISIOPATOLOGIA



Manipulation of Isoprenoid Biosynthesis as a Possible Therapeutic Option in Mevalonate Kinase Deficiency

Arthritis Rheum 2006; 54: 2306-13

Anakinra en HIDS
(Uso compasivo / Case Reports)

Anakinra is safe and effective in controlling hyperimmunoglobulinaemia D syndrome-associated febrile crisis

J Iinherit Metab Dis 2006; 29: 763

Treatment with anakinra in the hyperimmunoglobulinemia D/periodic fever syndrome

Rheumatol Int 2006; 27: 97-100

Mevalonate kinase deficiency syndrome with structural damage responsive to anakinra

Rheumatol 2007; 46: 1860-2

Anakinra en HIDS
(Uso compasivo / Case Reports)

On-demand anakinra treatment is effective in mevalonate kinase deficiency

Ann Rheum Dis 2011; 70: 2155-8

Efficacy of interleukin-1-targeting drugs in mevalonate kinase deficiency

Rheumatology 2012; 51: 1855-9

Mevalonate kinase deficiency in two sisters with therapeutic response to anakinra: case report and review of the literature

Clin Rheumatol 2014; 33: 1681-4

Síndrome de hiper-IgD

Canakinumab en síndrome de hiper-IgD

IL-1 y canakinumab

Base racional del ensayo clínico

Estructura del ensayo clínico

Long-term efficacy and safety of canakinumab treatment in active Hyper-IgD

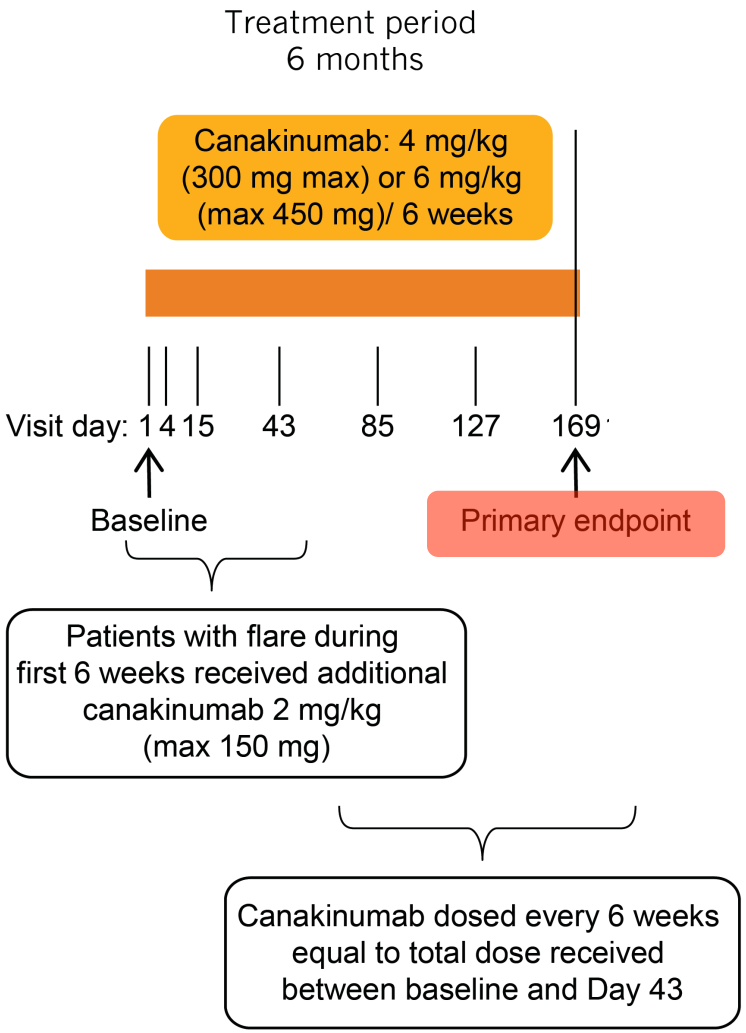
Results from an open-label study

NOVARTIS

ClinicalTrails.gov Identifier
NCT01303380

Ensayo canakinumab en HIDS

- Open-label single treatment arm study, with three well-defined parts:



Use of Canakinumab in the Cryopyrin-Associated Periodic Syndrome

Helen J. Lachmann, M.D., Isabelle Kone-Paut, M.D.,
Jasmin B. Kuemmerle-Deschner, M.D., Kieron S. Leslie, M.B., B.S.,
Eric Hachulla, M.D., Ph.D., Pierre Quartier, M.D., Xavier Gitton, Ph.D.,
Albert Widmer, M.Sc., Neha Patel, M.S., and Philip N. Hawkins, Ph.D., F.Med.Sci.,
for the Canakinumab in CAPS Study Group*

2 mg/kg q8w
(peso ≤40kg)

4 mg/kg q6w

Two Randomized Trials of Canakinumab in Systemic Juvenile Idiopathic Arthritis

Nicolino Ruperto, M.D., M.P.H., Hermine I. Brunner, M.D., Pierre Quartier, M.D.,
Tamás Constantin, M.D., Nico Wulffraat, M.D., Gerd Horneff, M.D., Riva Brik, M.D.,
Liza McCann, M.D., Ozgur Kasapcopur, M.D., Lidia Rutkowska-Sak, M.D.,
Rayfel Schneider, M.D., Yackov Berkun, M.D., Inmaculada Calvo, M.D.,
Muferet Erguven, M.D., Laurence Goffin, M.D., Michael Hofer, M.D.,
Tilmann Kallinich, M.D., Sheila K. Oliveira, M.D., Yosef Uziel, M.D., Stefania Viola, M.D.,
Kiran Nistala, M.D., Carine Wouters, M.D., Rolando Cimaz, M.D., Manuel A. Ferrandiz, M.D.,
Berit Flato, M.D., Maria Luz Gamir, M.D., Isabelle Kone-Paut, M.D., Alexei Grom, M.D.,
Bo Magnusson, M.D., Seza Ozen, M.D., Flavio Sztajnbok, M.D., Karine Lheritier, Ph.D.,
Ken Abrams, M.D., Dennis Kim, M.D., M.P.H., Alberto Martini, M.D.,
and Daniel J. Lovell, M.D., M.P.H., for the PRINTO and PRCSG*

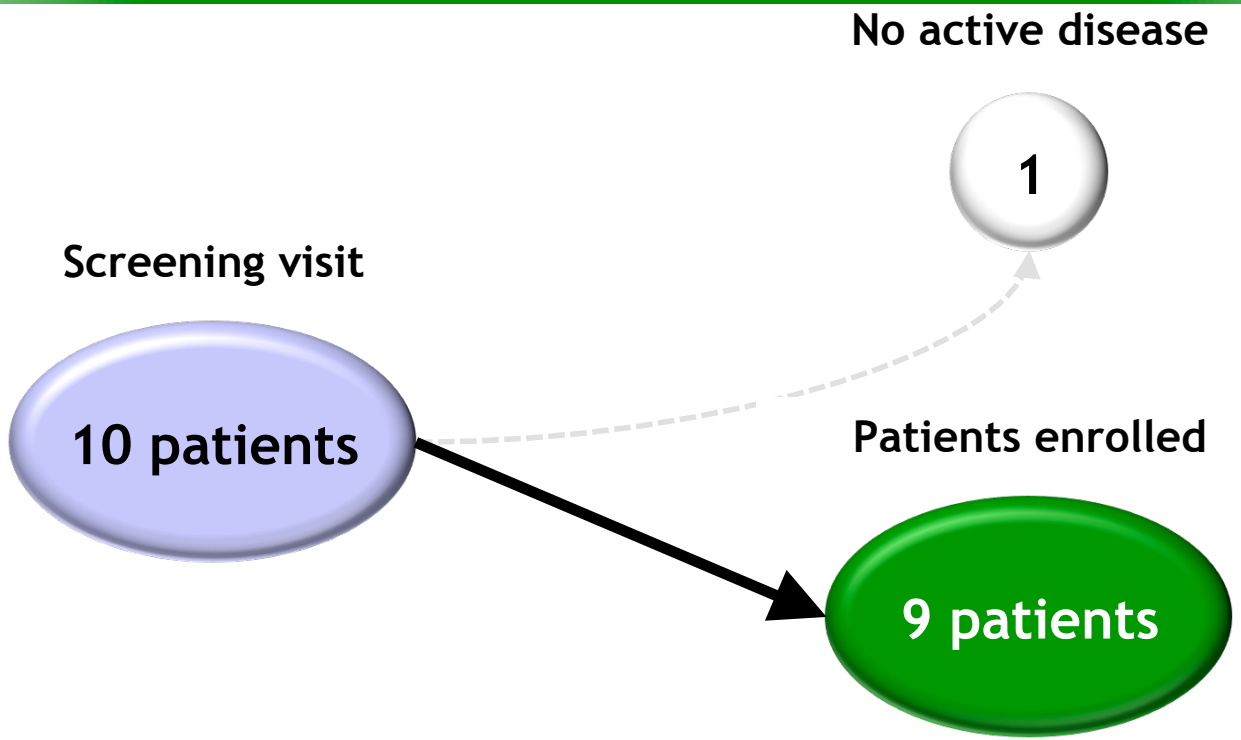
4 mg/kg q4w

Inclusion Criteria

- Patients older than 24 months at baseline
- Diagnosis of HIDS proven by DNA analyses (biallelic MVK mutations)
- Active HIDS (flare severity ≥2 and CRP values >10 mg/L)
- History of ≥3 febrile acute HIDS flares in the most recent 6-month period when not receiving prophylaxis treatment (**Historical period**)

Exclusion Criteria

- Pregnant or nursing (lactating) women
- Recurrent and/or active bacterial, fungal, or viral infections
- Positive microbiological results for:
    - •Hepatitis B surface antigen
    - •Hepatitis C antibody
    - •Tuberculosis and HIV screenings
- Immunocompromised patients
- Live vaccinations
- History of significant medical conditions
- Simultaneous use of etanercept, adalimumab, infliximab, anakinra or other investigational biologics.



- Sex: 6 female / 3 male.
- 100% Caucasian.
- Median ages:
  - . At baseline: 17.3 years (range 5-29 years).
  - . At HIDS diagnosis: 4.1 years (range 1-25 years).
- Three Spanish centers:
  - . H. La Fe (n: 5). Pediatric patients
  - . H. Sant Joan de Deu (n: 2). Pediatric patients.
  - . H. La Paz (n: 2). Adult patients



Primary objective

To assess the reduction in the frequency of flares during the 6-month treatment period compared with the historical period.

Secondary objectives

To assess :

- Occurrence of flares during the treatments periods (6-month and the 24-month long-term).
- Changes in flare duration (median days) during the trial, compared with the historical period.
- Changes in disease severity over time assessed by physician using a 5 point scale of severity score.
- Changes in the severity of the 4 main key signs and symptoms of HIDS.
- Time to flare after last canakinumab injection.
- Profiles of inflammatory markers (CRP, SAA) during the study.
- Adverse events reported during the study.

Síndrome de hiper-IgD

Canakinumab en síndrome de hiper-IgD

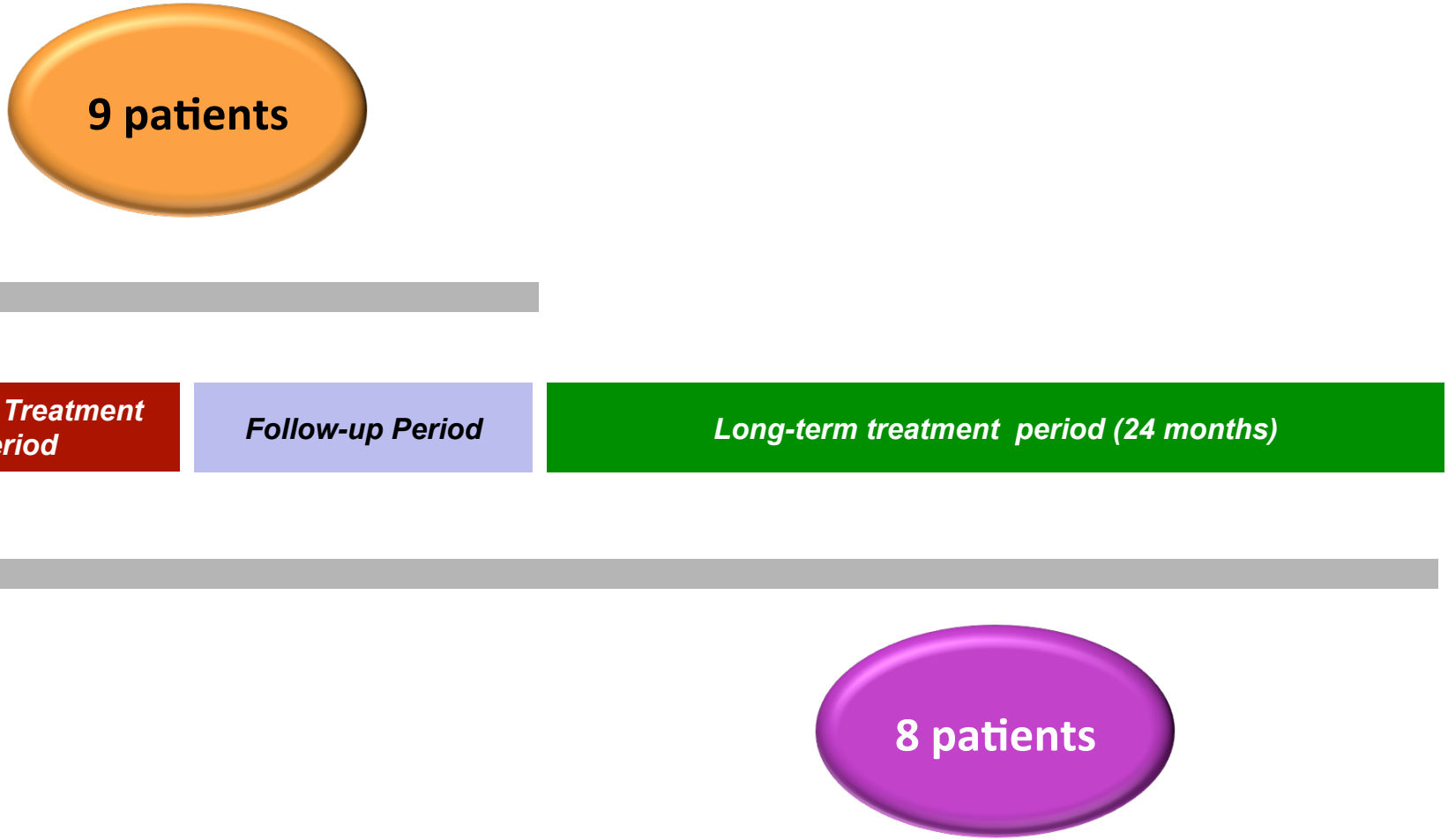
IL-1 y canakinumab

Base racional del ensayo clínico

Estructura del ensayo clínico

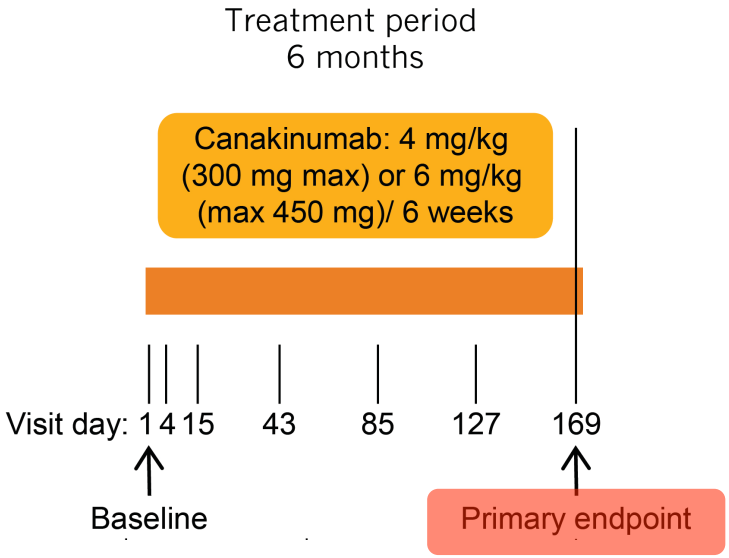
Resultados: Eficacia

Ensayo canakinumab en HIDS



Ensayo canakinumab en HIDS

The ***primary objective*** was to assess the ***efficacy of canakinumab to reduce the flare rate*** in patients with HIDS during the 6-month treatment period compared with that from the historical period (the most recent 6-month period in which patients did not receive drugs other than symptomatic treatment with NSAIDs and/or steroids)



The ***primary objective*** was to assess the ***efficacy of canakinumab to reduce the flare rate*** in patients with HIDS during the 6-month treatment period compared with that from the historical period (the most recent 6-month period in which patients did not receive drugs other than symptomatic treatment with NSAIDs and/or steroids)

	Historical period	Treatment period
Median number of flares	5	0
Range	3-12	0-2
Total number of flares	59	3
Patients with flares (n)	9	2

Patients who required dose up-titration at week 6 according to protocol.

- 1 patient with mild-to-moderate flare
- 1 patient with mild flare

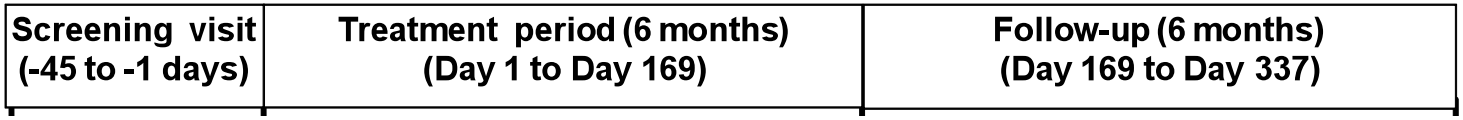
No flares afterwards during treatment period

Ensayo canakinumab en HIDS

6 month Treatment Period	Follow-up Period	Long-term treatment period (24 months)	
		1st year	2nd year
patients: 2 / 9 **total flares: 3** mild: 1 mild-moderate: 2		**patients: 4 / 8** **total flares: 6** minimal: 2 mild: 4	**patients: 2 / 8** **total flares: 2** minimal: 1 mild: 1

Secondary objectives

1. Time to flare after the last canakinumab injection dose





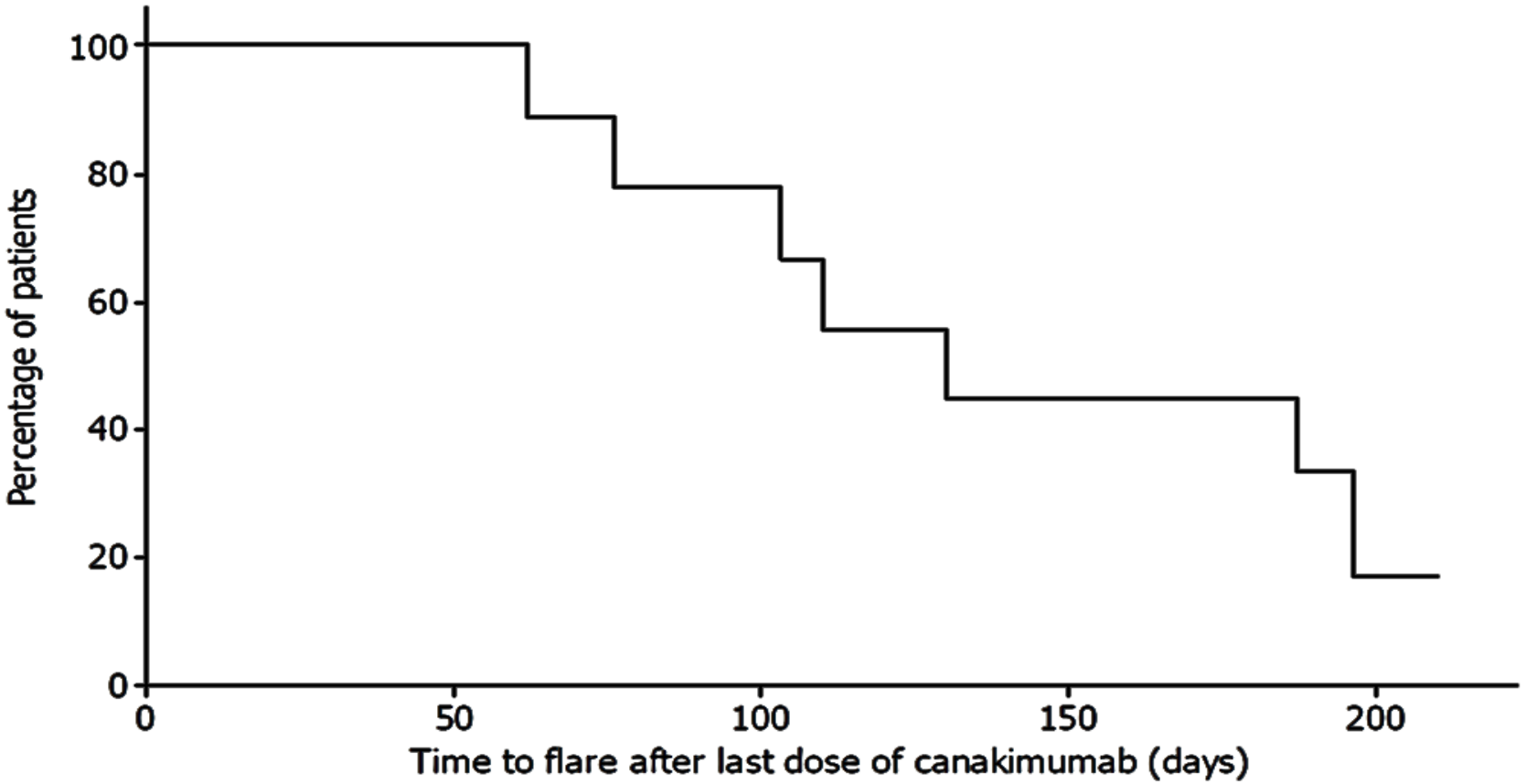


Flares during Follow-up period
- 4 mild
- 3 moderate

No flares during 6 months Follow-up period

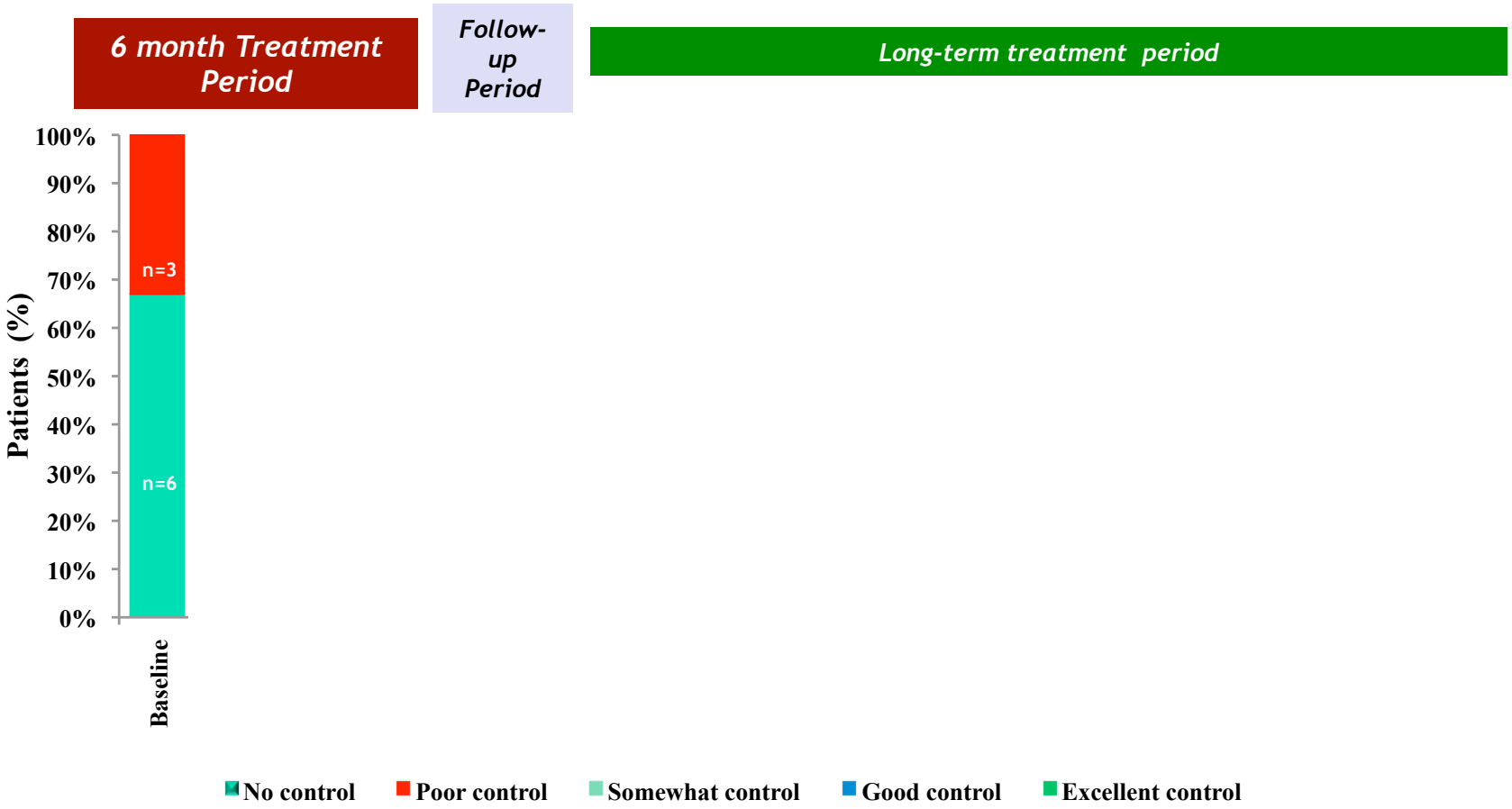
Median time to flare	110 days
Range	62-196 days

Ensayo canakinumab en HIDS



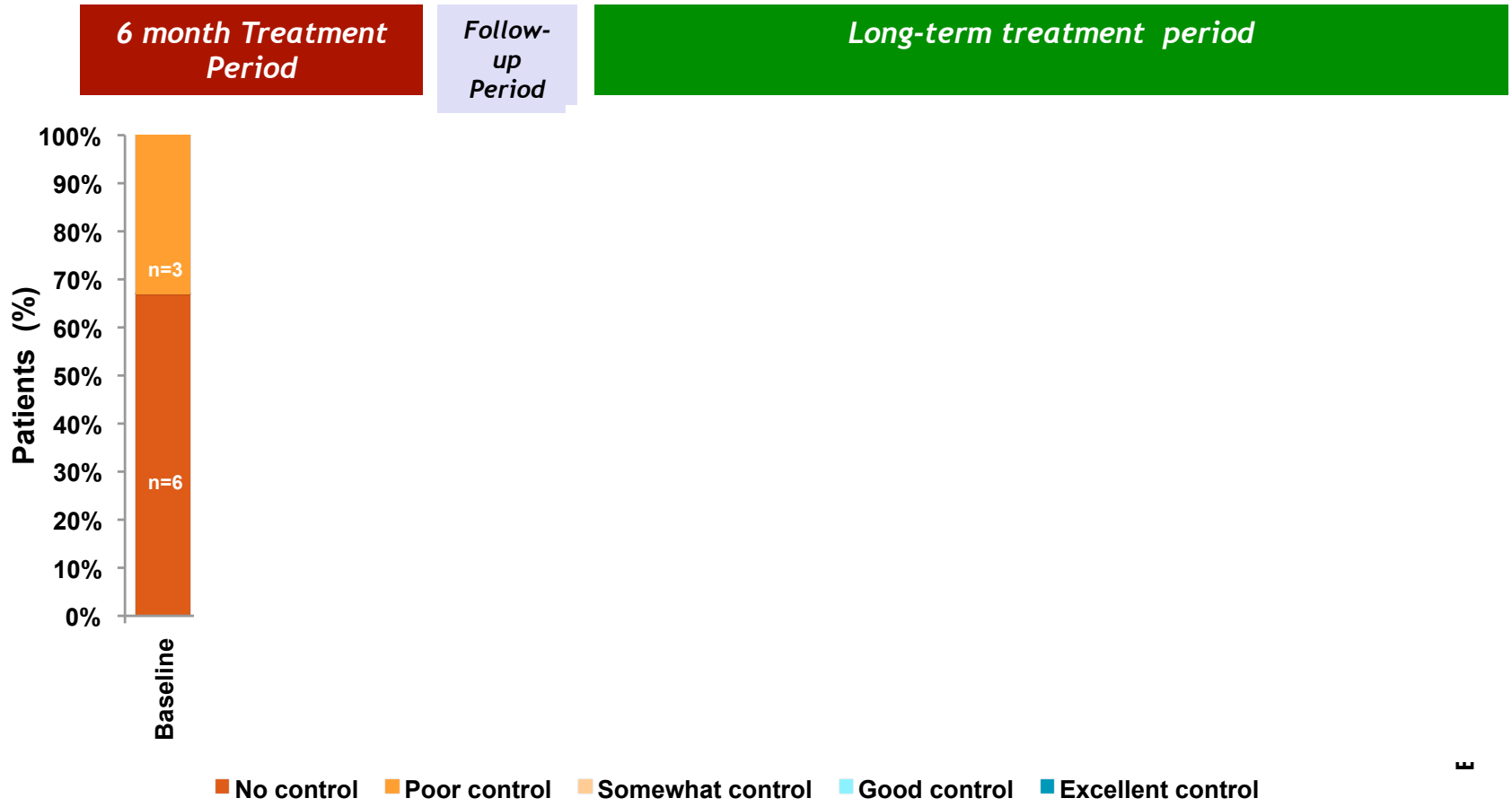
Secondary objectives

1. Time to flare after the last canakinumab injection dose
2. Disease control during treatment period



Secondary objectives

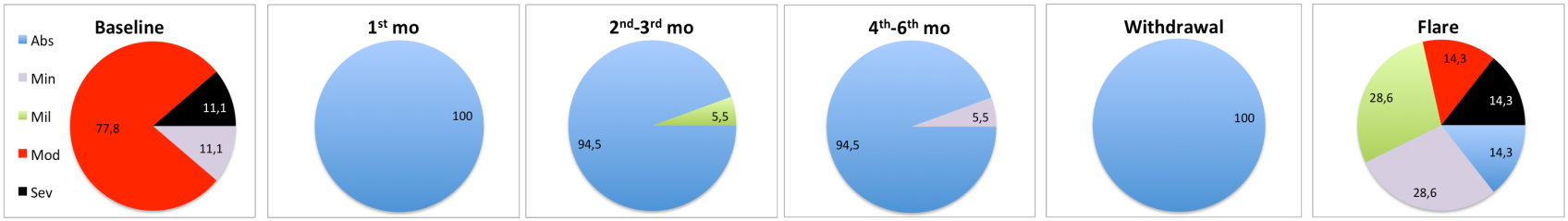
1. Time to flare after the last canakinumab injection dose
2. Disease control during treatment period



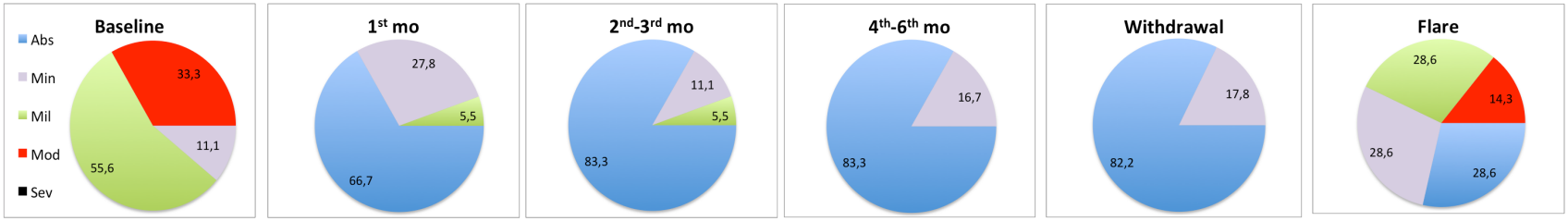
Ensayo canakinumab en HIDS

Fever

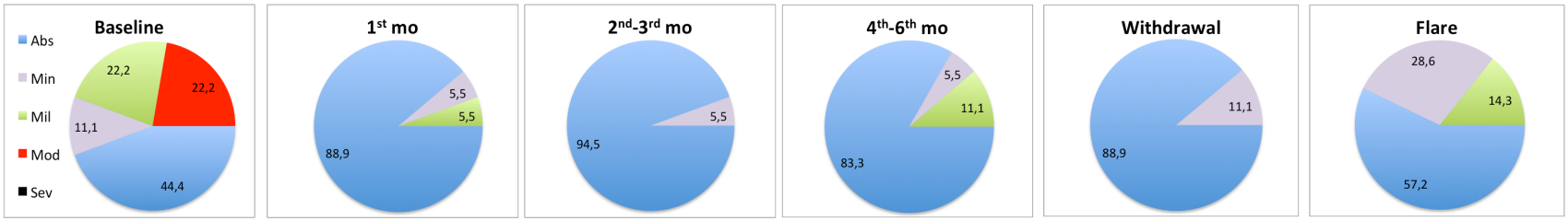
6-month treatment period



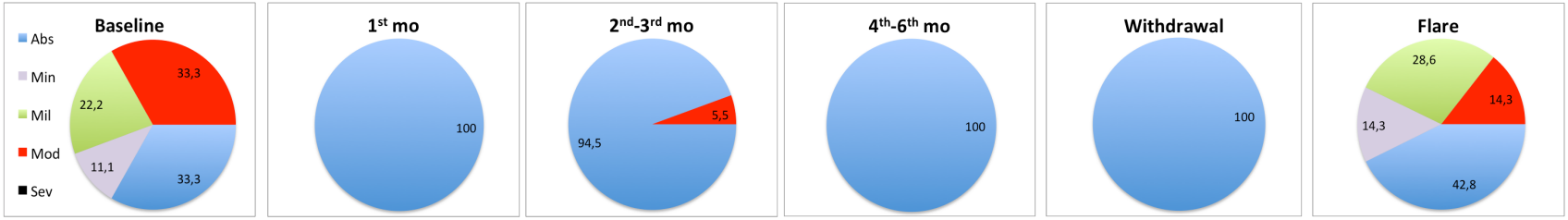
Lymphadenopathy



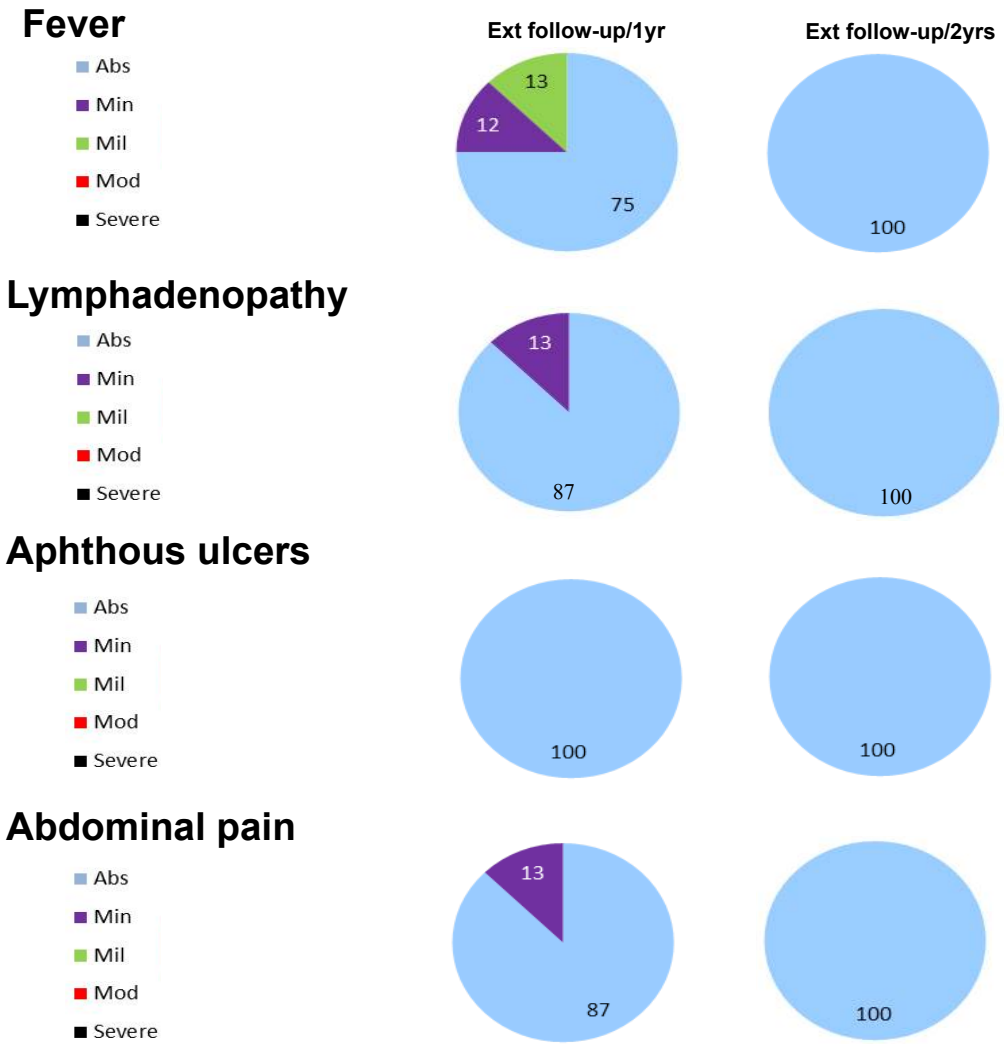
Aphthous ulcers



Abdominal pain

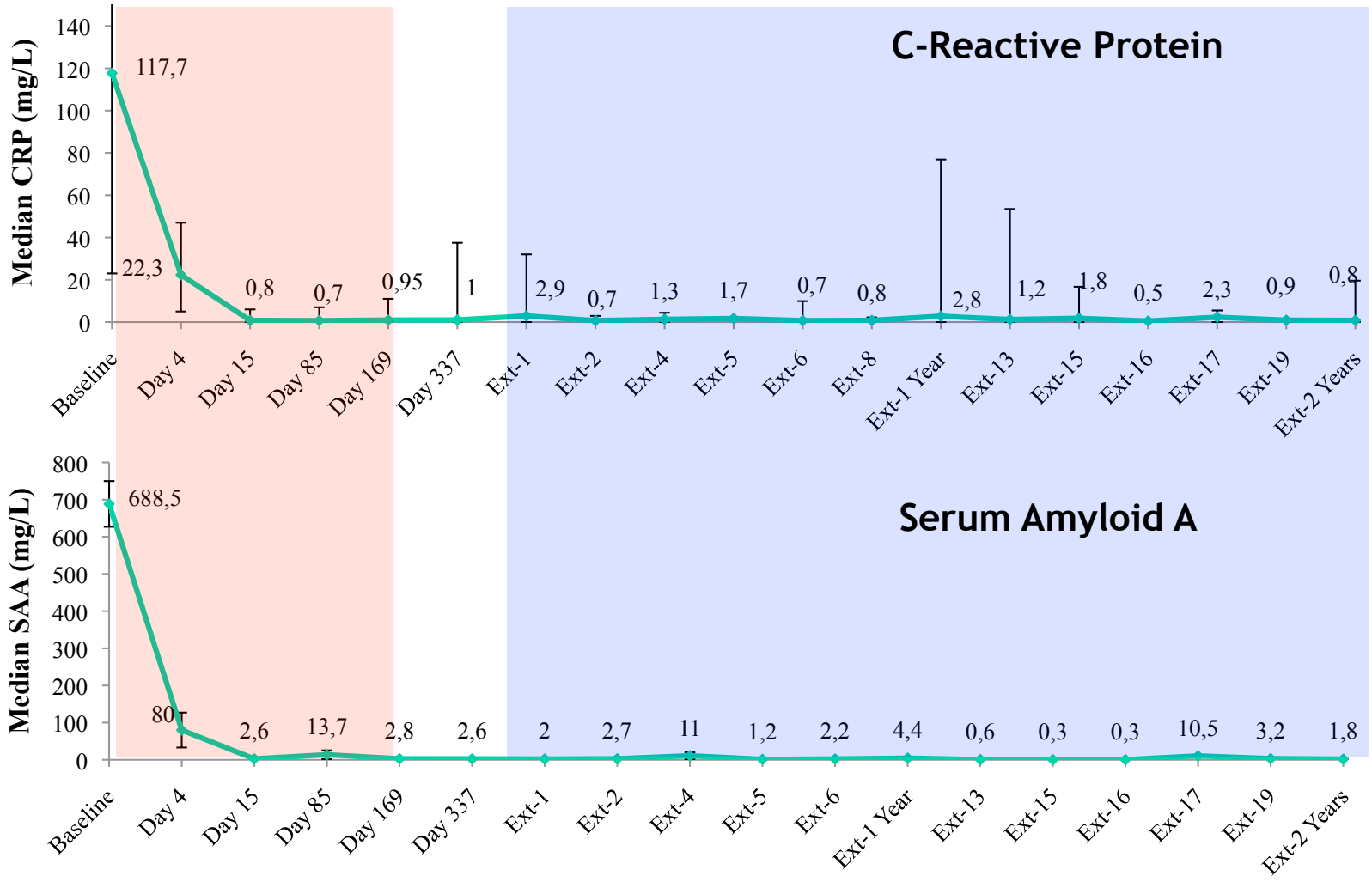


Ensayo canakinumab en HIDS



Secondary objectives

1. Time to flare after the last canakinumab injection dose
2. Disease control during treatment period
3. Changes in the 4 key disease features
4. Changes in laboratory parameters



Normal range
(<10 mg/L)

Síndrome de hiper-IgD

Canakinumab en síndrome de hiper-IgD

IL-1 y canakinumab

Base racional del ensayo clínico

Estructura del ensayo clínico

Resultados: Eficacia

Resultados: Seguridad

Safety

Adverse events (AEs) were reported in all enrolled patients

- No deaths occurred
- No AEs led to drug discontinuation
- Usually AEs were of mild (76%) or moderate intensity
- Urinary tract infections were the most common AEs reported
- Only one adverse event (vulvovaginal mycotic infection) was considered to be drug related by physician in charge.

Common adverse events presented (≥2 patients)	Patients n (%)
Number of patients with AE(s)	9 (100)
Primary system organ class	
Infections and infestations	9 (100)
Gastrointestinal disorders	6 (67)
General disorders and administration site conditions	6 (67)
Musculoskeletal and connective tissue disorder	4 (44)
Skin and subcutaneous tissue disorders	4 (44)
Eye disorders	2 (22)
Nervous system disorders	2 (22)

Safety

Four patients reported serious AEs

- One patient required hospitalization for a HIDS flare
- One patient suffered from chronic headache
- One patient suffered from temporomandibular dysfunction

- One patient suffered from a gastrointestinal bleeding, severe anaemia and from a peritonitis
    - She suffered from AA amyloidosis, requiring peritoneal dialysis

Síndrome de hiper-IgD

Canakinumab en síndrome de hiper-IgD

IL-1 y canakinumab

Base racional del ensayo clínico

Estructura del ensayo clínico

Resultados: Eficacia

Resultados: Seguridad

Conclusiones

- Canakinumab treatment substantially reduced the frequency of acute inflammatory flares in patients with active HIDS

•Canakinumab demonstrated rapid disease control for both clinical signs and symptoms as well as serologic response during the treatment phase, which was maintained through the 24 month long-term treatment.

•No unexpected safety findings were observed during the entire study period (treatment, follow-up and long-term)

•Safety profile was consistent with that observed in other canakinumab studies