Umbrella study design in patients with Hereditary Periodic Fevers, an orphan autoimmune disease

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Outline

- Hereditary Periodic Fevers
- Canakinumab
- Study design
- Conclusion

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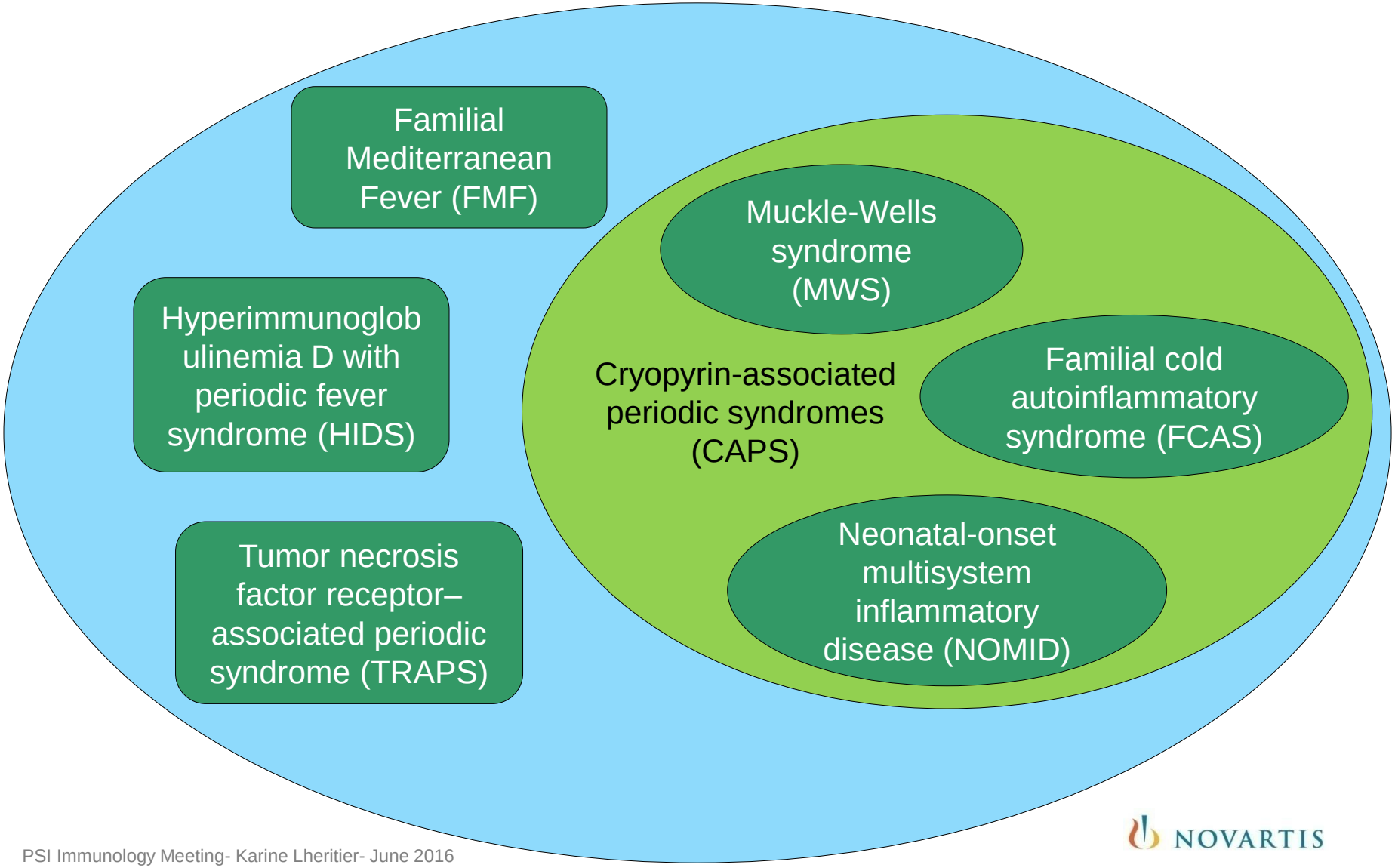
Hereditary Periodic Fevers

Rare and distinct heritable disorders

- Hereditary periodic fever (HPF) syndromes are rare and distinct heritable disorders characterized by:
  1. Short and recurrent attacks of fever
  2. Severe localized inflammations that occur periodically or irregularly and are not explained by usual childhood infections.
- Between attacks, patients feel well and regain their normal daily functions until the next episode occurs.
- The episodes are usually associated with elevated serum levels of acute-phase reactants (e.g., fibrinogen, serum amyloid A [SAA]), an elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and leukocytosis.
- The term of periodic fever syndromes includes a group of clinically distinct autoinflammatory conditions (Koyfman et al 2013; Federici et al 2015):

Hereditary Periodic Fevers

Cluster of orphan auto-immune diseases



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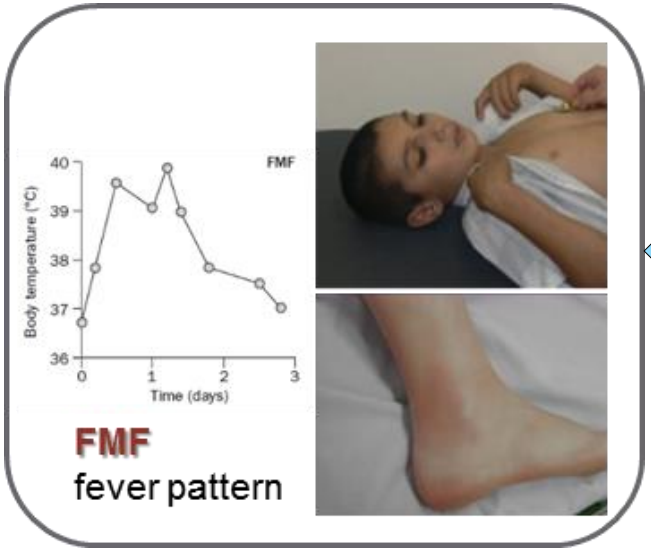
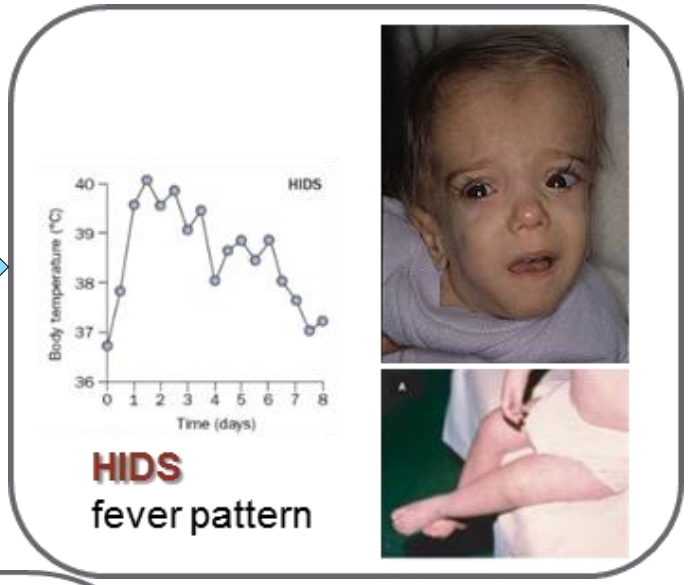
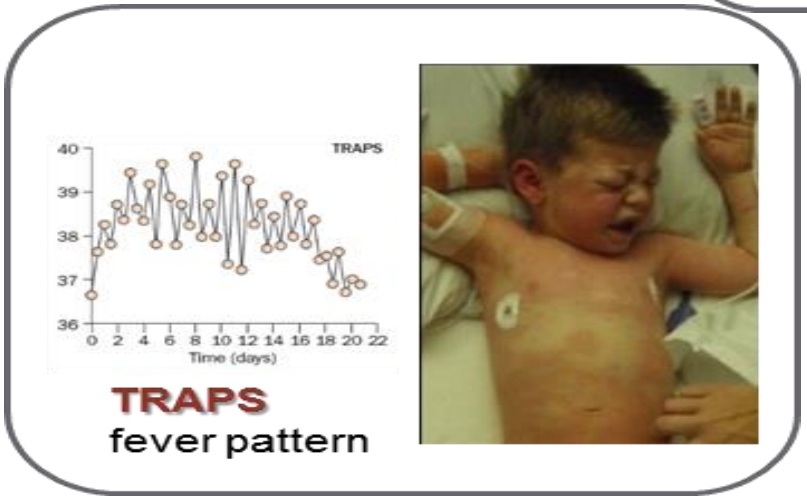
Hereditary Periodic Fevers syndromes – Disease background

Significant unmet medical need exists in HPF Syndromes crFMF, TRAPS and HIDS



Different clinical presentation





FMF = familial Mediterranean fever; **HIDS** = Hyperimmunoglobulin D syndrome; **TRAPS** = Tumor necrosis factor receptor-1 associated periodic syndrome

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Hereditary Periodic Fevers

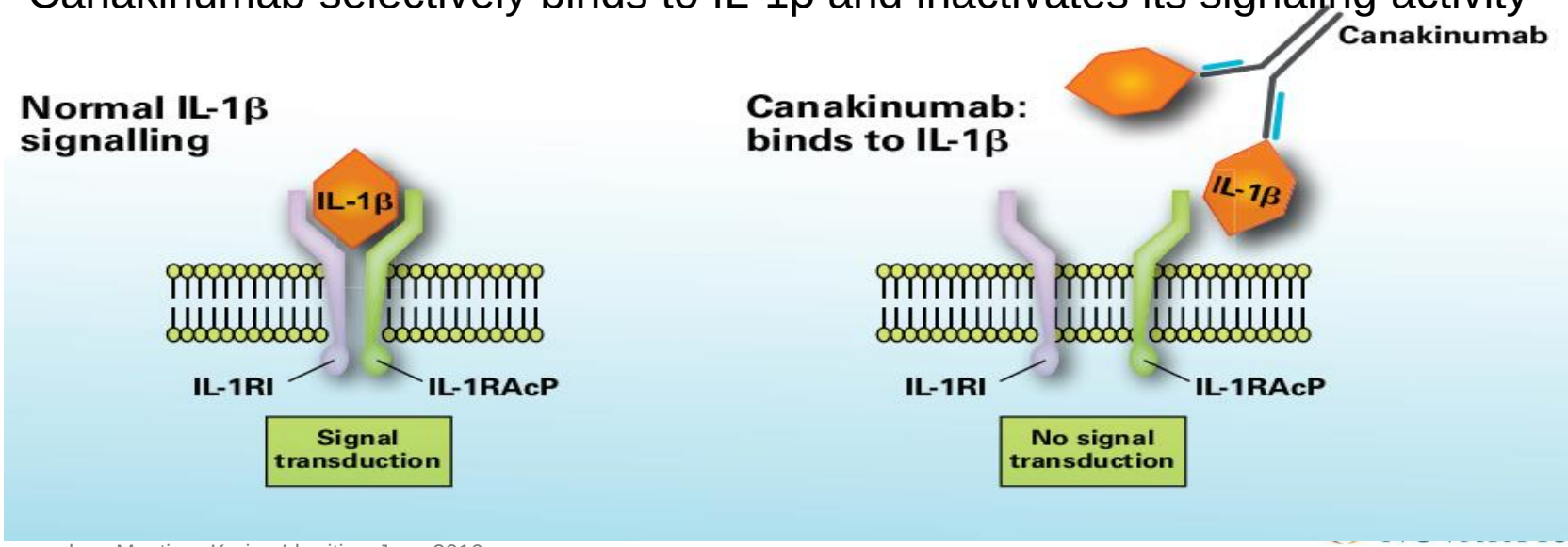
Dysregulation of IL-1β production and No approved treatment

- These conditions can be grouped based on their common pathophysiology driven by dysregulation of IL-1β production and shared clinical features of recurrent episodes of inflammation and fever.
- Although the underlying genetic defects and molecular etiology differ across the periodic fever syndromes, the disease mechanism common across these autoinflammatory conditions involves abnormal activation of the innate immune system, leading to dysregulation of cytokines and excessive inflammation (Ozen and Bilginer 2014).
- There are currently no approved treatments for colchicine resistant/intolerant (cr)-FMF, HIDS and TRAPS.
- **However** Canakinumab treatment has already been shown to be effective and has been approved in treating CAPS patients.

Canakinumab (Ilaris®)

The drug: Anti-IL-1β

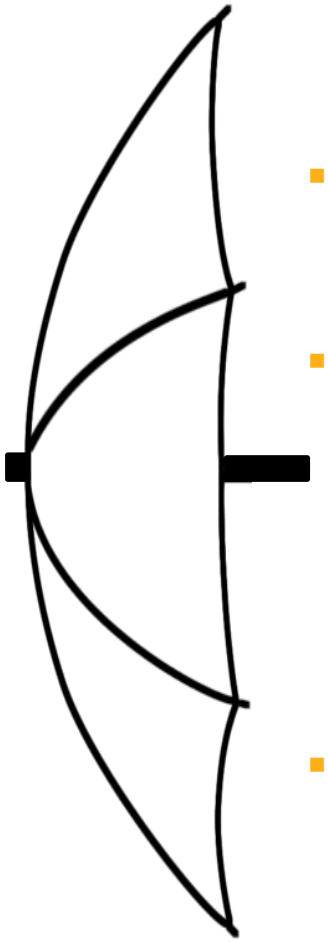
- IL-1β is a key mediator of the inflammatory response in all the classical periodic fever syndromes
- Canakinumab is an anti-interleukin-1β monoclonal antibody being developed for the treatment of IL-1β - driven inflammatory diseases
- The genes which are mutated in FMF, HIDS and TRAPS are identified, and the effect of the altered protein to activate IL-1β secretion and cause inflammation is established
- Canakinumab selectively binds to IL-1β and inactivates its signaling activity



Church LD, McDermott MF. *Expert Rev Clin Immunol.* 2010;6:831-41. Lachmann HJ, et al. *Arthritis Rheum.* 2011;63:314-24.

Phase III study design

Unprecedented phase III umbrella program targeting 3 indications



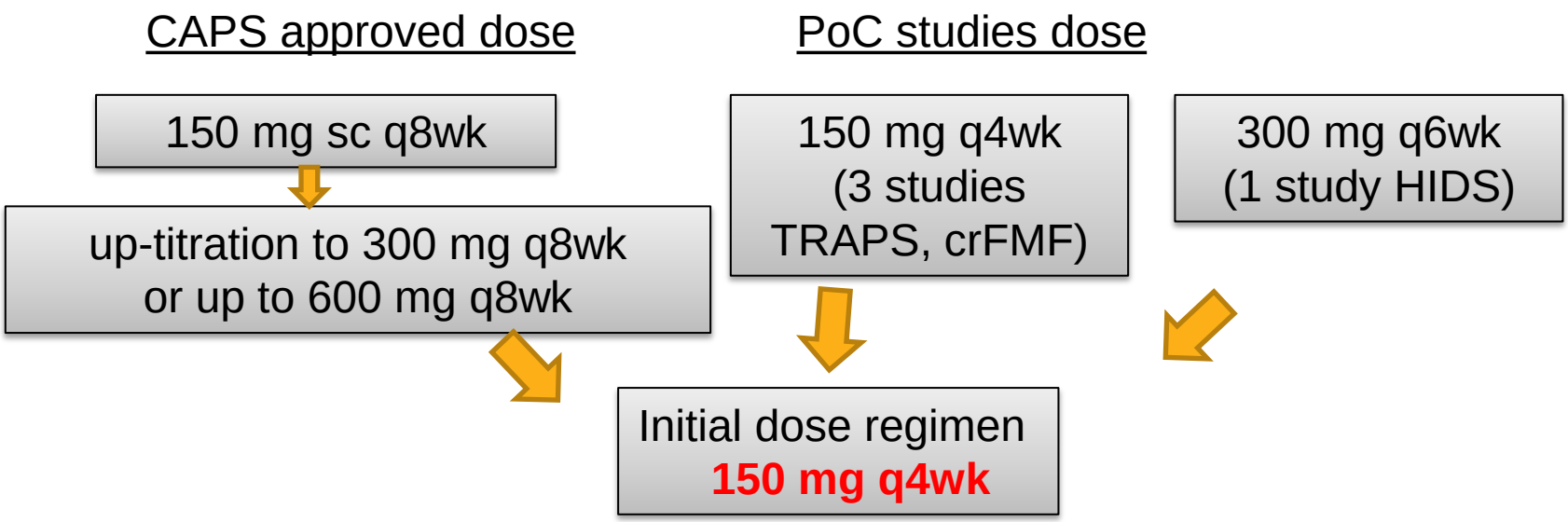
- Background: 4 PoC, open label studies in patients treated with Canakinumab for TRAPS, HIDS, and cr- FMF have preliminary demonstrated efficacy and safety.
- These preliminary encouraging results warranted the further assessment of the benefit/risk of Canakinumab treatment in a Phase III program in patients suffering from these 3 rare conditions in one study called Umbrella study.
- Objectives discussed and supported by HA (EMA, FDA and PMDA) for the 3 cohorts:
  - To show superiority of Canakinumab relative to placebo with respect to % of responders
  - To maintain a clinically meaningful response
  - Long-term safety

  ⇨ study with several epochs for 3 cohorts
- In parallel, several challenges:
  - dose selection,
  - primary endpoint definition,
  - sample size consideration,
  - how to analyze the data.

Phase III study design - dose selection

Starting dose 150 mg q4wk with up-titration

- No formal dose finding conducting due to the rarity of the 3 conditions



  - to harmonize exposure across the 3 conditions,
  - and up-titration to 300 mg q4wk to optimize the regimen in order to achieve efficacy in difficult cases.

- However reduced frequency dose 150 mg sc q8wk is evaluated in the randomized withdrawal epoch to assess if clinical efficacy can be maintained (with up-titration to 300 mg q8wk)

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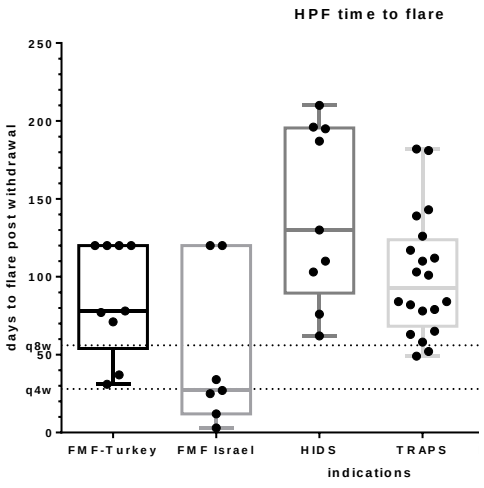
Phase III study design - primary efficacy endpoint

Co-Primary endpoint with 2 different timepoints

- Primary efficacy endpoint defined based on PoC studies and CAPS results
- Rapid response in CAPS

(1) Resolution of index flare at Day 15

- In 4 PoC studies, >2/3 of patients flare after12 weeks after last dose



(2) No new flare from the resolution of the index flare until Week 16

Responder definition

(co-primary endpoints)

(1) Resolution of index flare at Day 15
   a) Physician's global assessment (PGA) <mild , AND
   b) CRP normalization or 70% reduction

AND

(2) No new flare from the resolution of the index flare until Week 16 (PGA ≥mild and CRP ≥30 mg/L)

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Phase III study design - Sample size

60 patients per disease cohort

- The sample size was <u>separately</u> calculated for each cohort (cr-FMF, HIDS, TRAPS) but with <u>same</u> assumptions
- Hypotheses: H_{1j}: $p_{1j} - p_{2j} = 0$ versus H_{Aj}: $p_{1j} - p_{2j} \neq 0$ where j = 1, 2, 3 for each of the cohorts
- Uncertainty on
  - the minimum clinically important difference (MCID) between Canakinumab and Placebo with respect to % of responders 45%
  - placebo response rate

➢ 60 patients per disease cohort

- Difficulty in recruiting TRAPS patients due to the ultra-orphan nature of the disease (0.01:10,000 people affected in the EU; 10,000 people worldwide) and the lower flare frequency.
  - 46 TRAPS patients (representing 80% of the required sample size) were randomized providing for 83% power to detect a between-treatment difference of 45%.

Phase III study design - Objectives

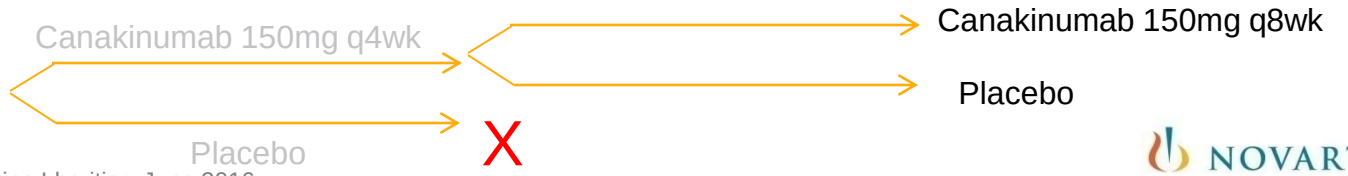
Refinement of Objectives

Final objectives : to determine

- Whether Canakinumab at a starting dose of 150 mg s.c. q4wk is able to induce and maintain a clinically meaningful reduction of disease activity after 16 weeks of treatment in a greater proportion of patients with TRAPS, HIDS, or crFMF compared to placebo.

- The efficacy and safety of a dose individualization (up-titration) up to a maximum of 300 mg q4wk, in case of lack or incomplete response to the initial dosing regimen.

- In patients responding to the initial dosing regimen of every 4 weeks, canakinumab will maintain its clinical efficacy if administered at a prolonged dosing interval of 150 mg s.c. q8wk



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Phase III study design - Objectives

Different Key objectives in each Epoch

Epoch 1	Epoch 2	Epoch 3	Epoch 4
Screening Phase	16 Weeks, Double-blind, Randomized, Placebo-controlled	24 Weeks, Randomized, Withdrawal Period	72 Weeks, Open-label Maintenance/Dose Reduction Period

- Up to 12 weeks for the patient to flare

- To demonstrate superiority of canakinumab 150 mg q4w vs placebo in reducing disease activity
- To evaluate the clinical remission with PGA and serological remission
  - CRP ≤10 mg/L
  - SAA ≤10 mg/L
- To evaluate the safety of canakinumab

- To evaluate the % of Canakinumab responders in Epoch 2 who maintain a clinically meaningful response when switched to canakinumab qw8k compared to placebo

- To evaluate the long-term safety and tolerability and immunogenicity of canakinumab

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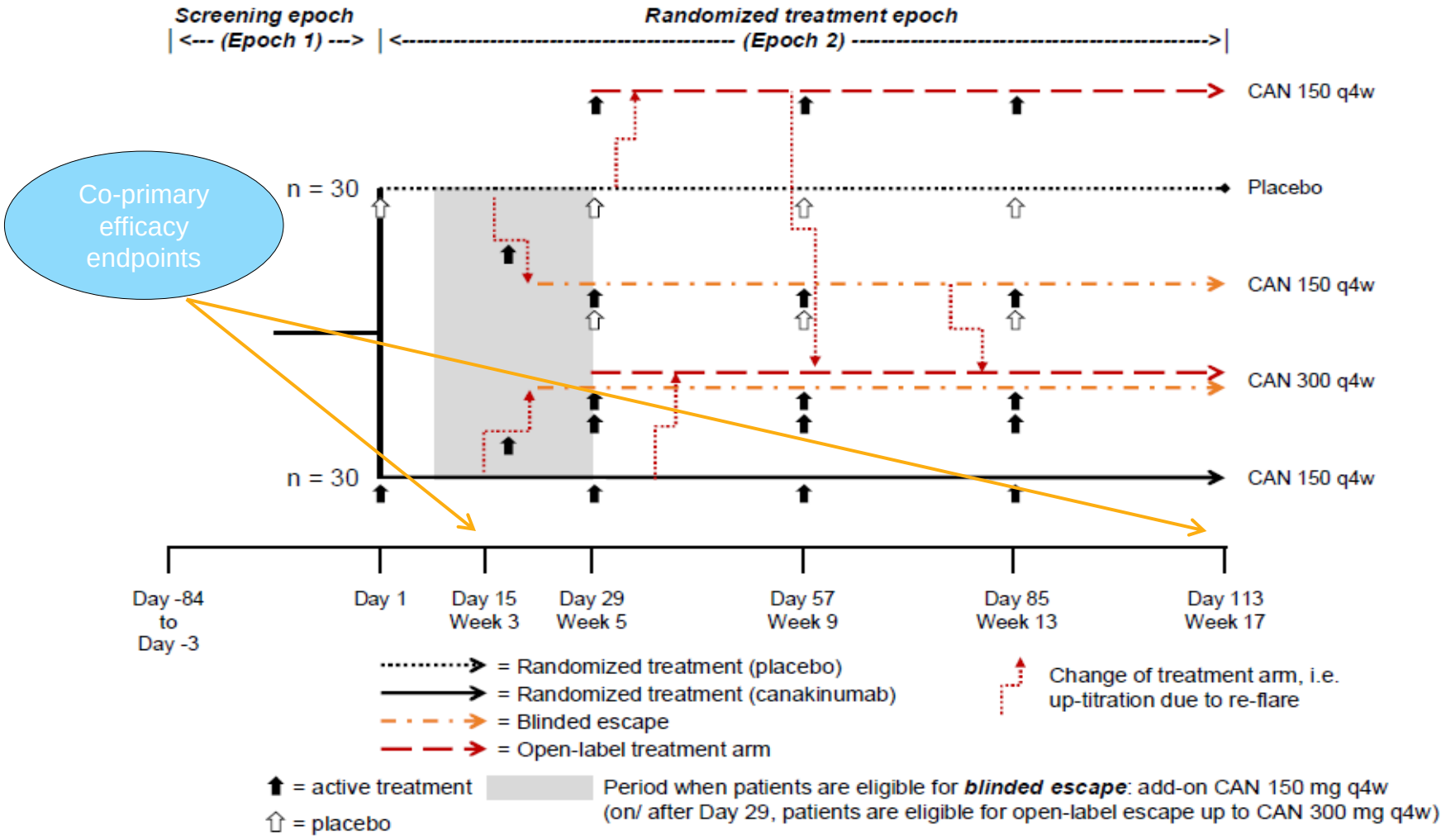
Phase III study design - Epoch 1 & 2

Randomized treatment part (16 weeks); starting dose 150mg q4wk



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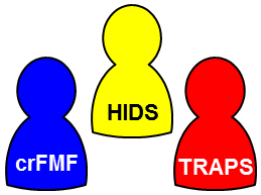
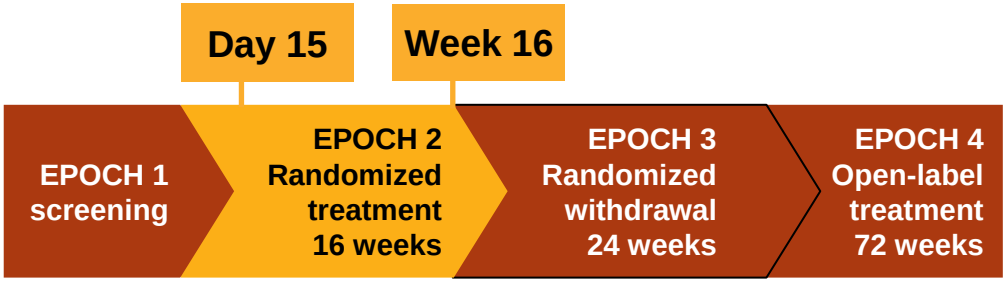
Phase III study design - Primary objective

Primary objective agreed with FDA, CHMP and PMDA





Primary objective

To demonstrate superiority of canakinumab 150 mg q4w vs placebo in reducing disease activity by resolving flare by Day 15 and inhibiting new flares over 16 weeks of treatment

- To avoid any issues with unblinding, patients having any up-titration or who discontinue in Epoch 2 are considered as non-responder

If the primary objective is achieved, all secondary endpoints in the randomized treatment epoch is assessed in a hierarchical testing procedure to evaluate the superiority of canakinumab s.c. q4wk over placebo.

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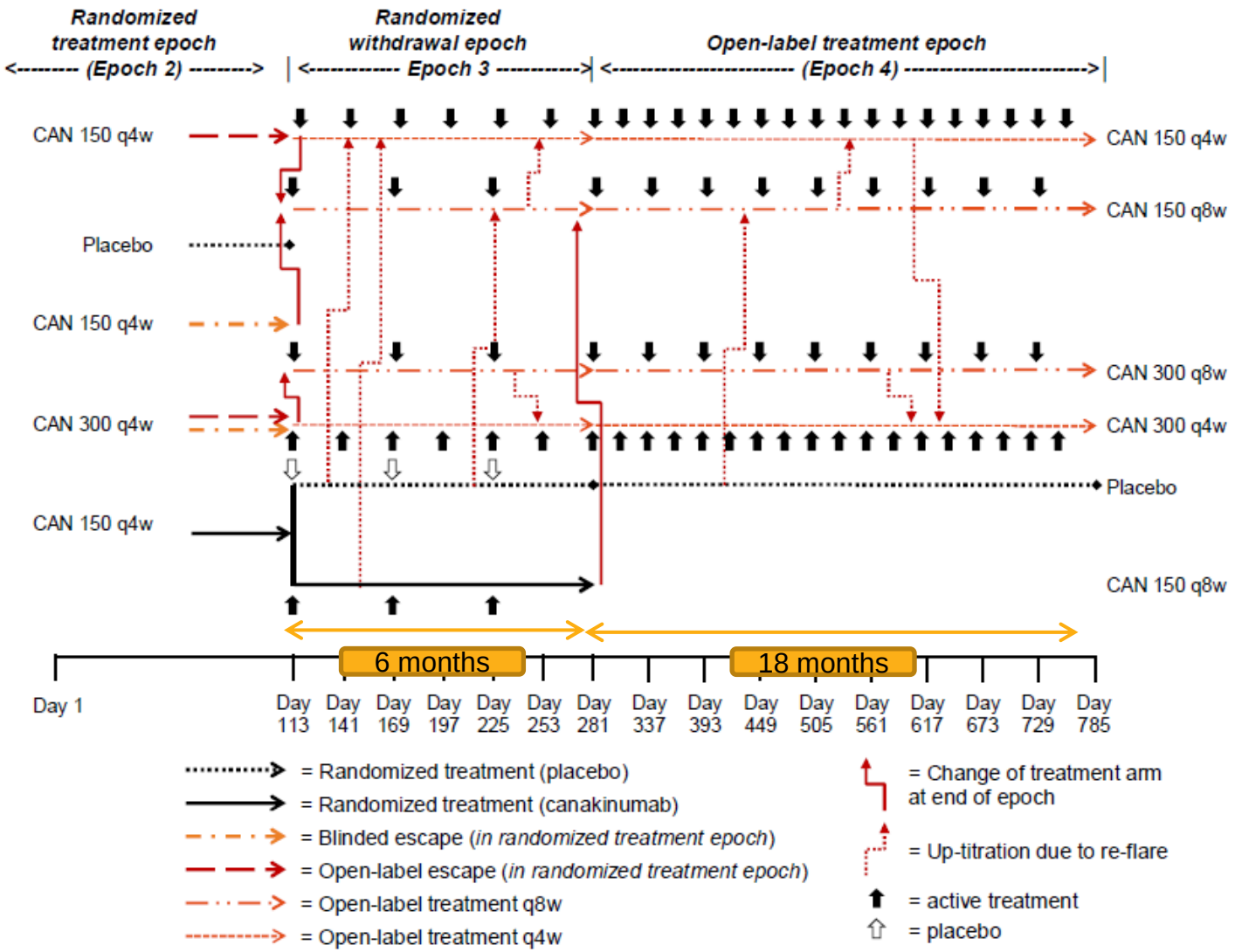
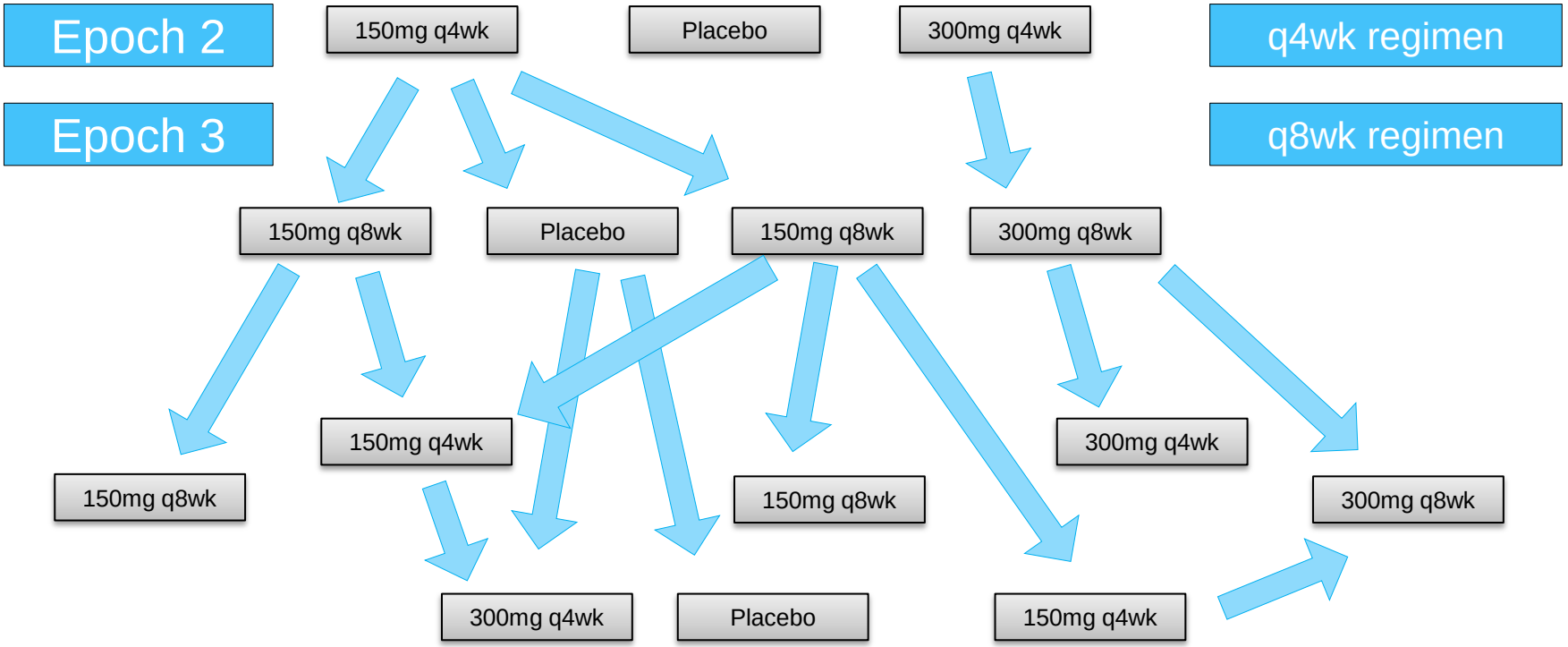
Phase III study design - Epoch 3 & 4

Randomized withdrawal (with 150mg q8wk) & Open-label treatment parts



Phase III study design - How to analyze the data

Consider Cumulative dose for the analysis



Almost more dose options than patients!!

Solution

Cumulative dose used in analyses in randomized withdrawal & open label epochs

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Phase III study design - Additional requests

Non-randomized patients added to the design

1. Request from PMDA
   - One of the inclusion criteria for crFMF patients:

   "At least one of the known MEFV gene exon 10 mutations"

   PMDA requested to add Japanese crFMF patients with non-exon 10 mutations due to bigger population in Japan

2. Request from the PDCO at the European Medicines
   - To include patients >28 days in this clinical trial compared to previously ≥2 years of age.

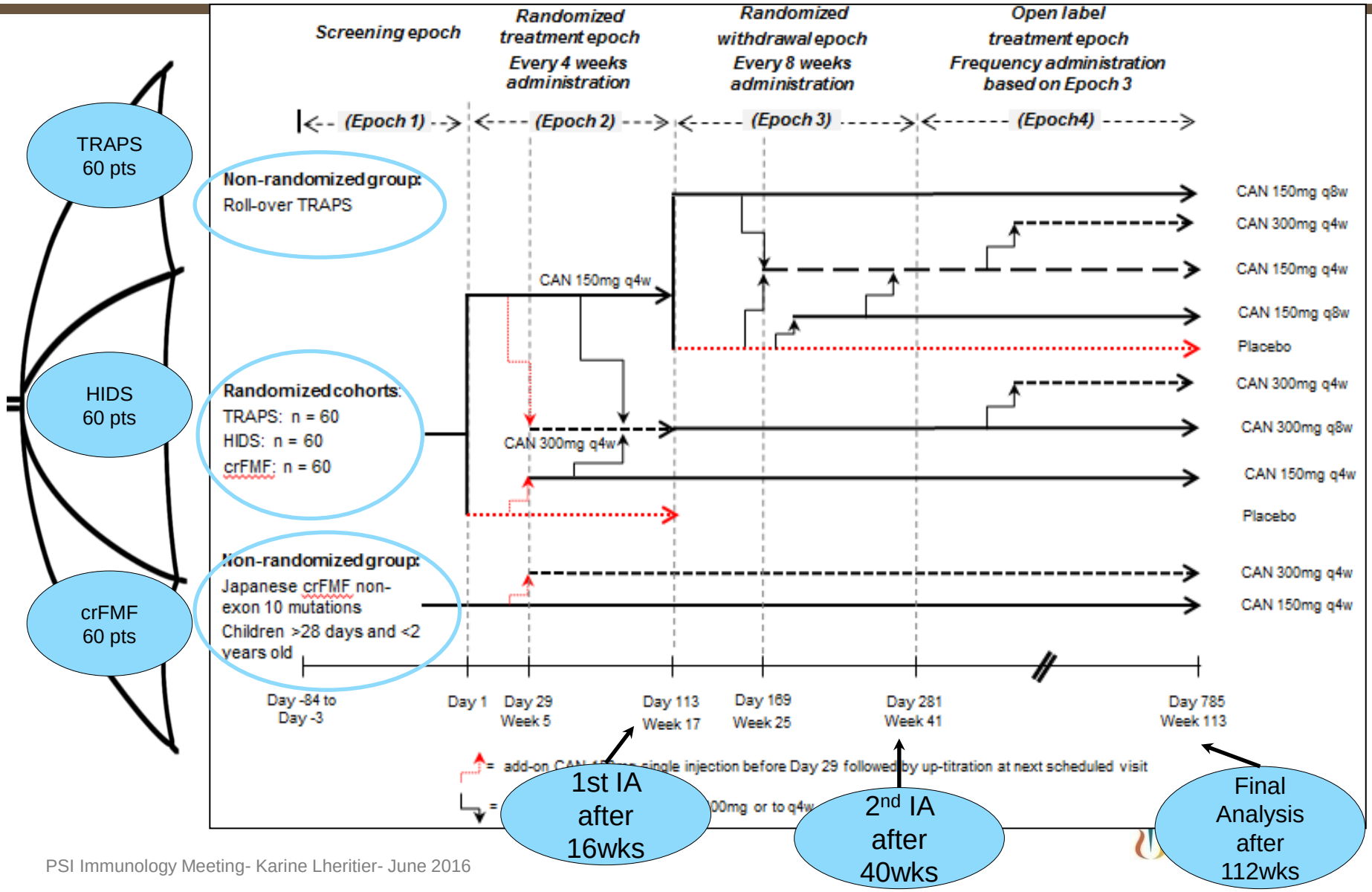
1)+2) ⇨ Japanese crFMF patients with non-exon 10 mutations & patients >28 days but <2 years old entered the study directly into the open-label arm in the randomized treatment part as non-randomized patients

3. Request from countries (UK, Italy)
   - In order to provide access to treatment, roll-over TRAPS patients previously participating in clinical studies

3) ⇨ These patients were allowed to enter the study in the randomized withdrawal part as non-randomized patients

Phase III study design - Final design

Pivotal umbrella study for crFMF, HIDS and TRAPS



Any questions?

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