Clinical Trial Design

Olivier Boyer MD, PhD

INSERM U1234 Pathophysiology, Autoimmunity and Immunotherapy

FOCIS Center of Excellence Pan'THER

Rouen, France

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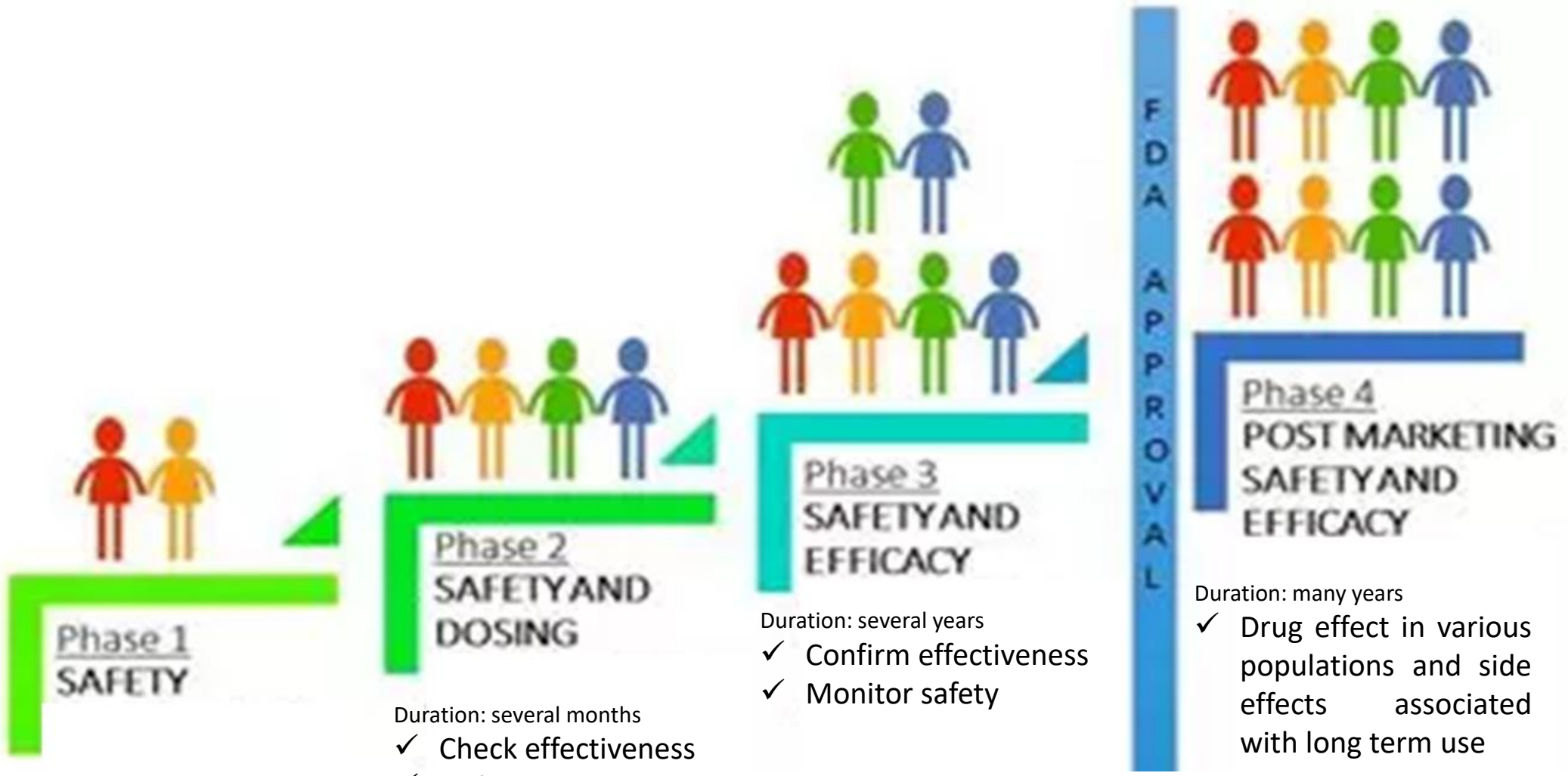
Acknowledgements: P Joly, MD, PhD ; V Hebert, MD, PhD ; B Diquet, MD, PhD

Phases of clinical trials (CT)



Duration: several months

- ✓ Evaluate safety

Duration: several months

- ✓ Check effectiveness
- ✓ Define dose
- ✓ Further evaluate safety

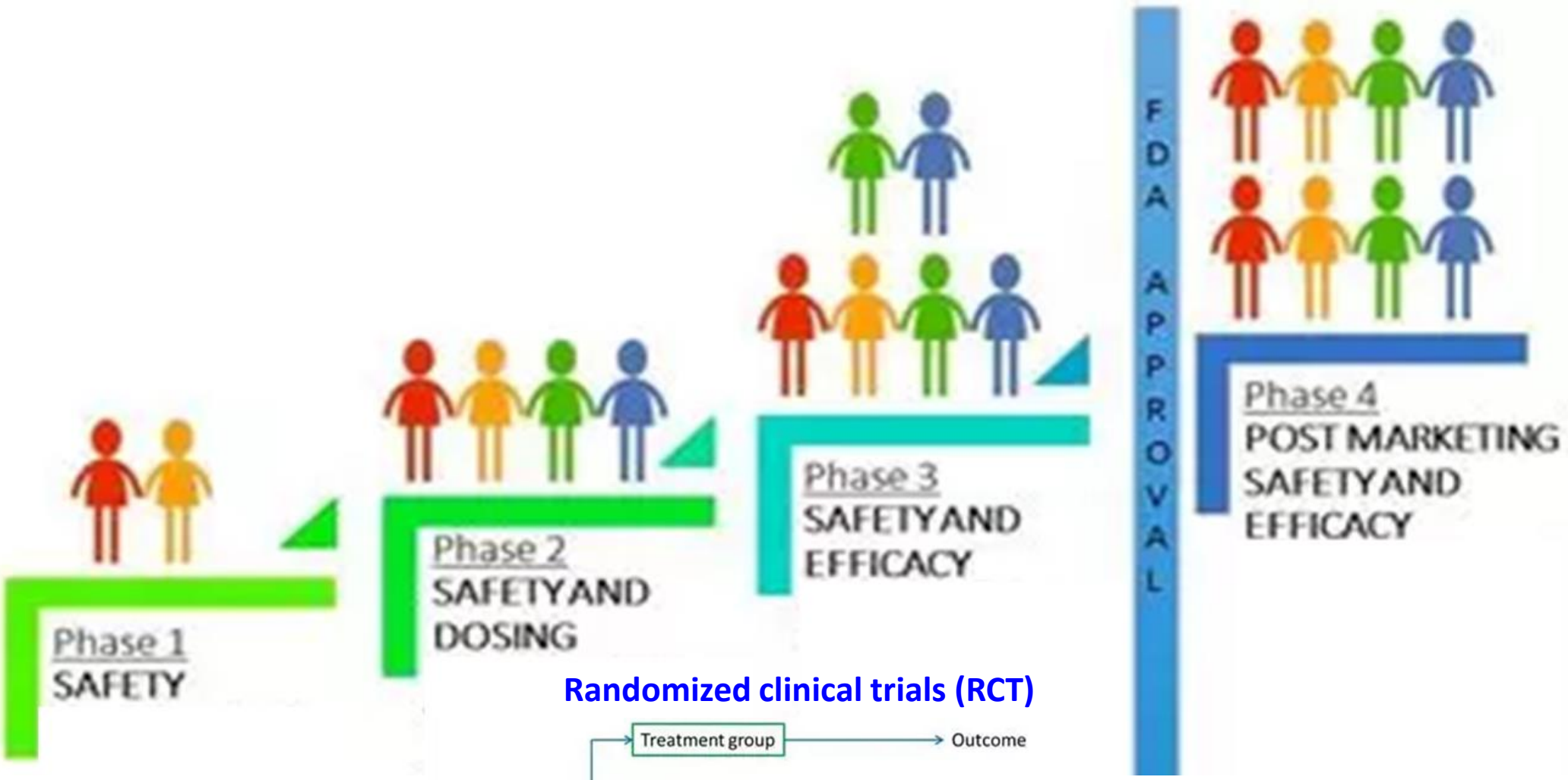
Duration: several years

- ✓ Confirm effectiveness
- ✓ Monitor safety

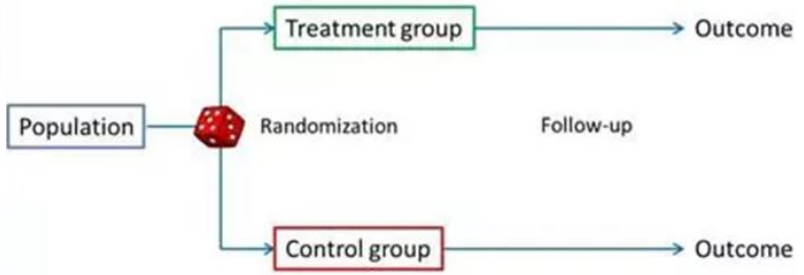
Duration: many years

- ✓ Drug effect in various populations and side effects associated with long term use

Phases of clinical trials (CT)



Randomized clinical trials (RCT)



Phases of clinical trials (CT)

Let's not neglect therapeutic advances resulting from the simplest methodology

- Case reports and case series are considered providing the lowest degree of scientific evidence

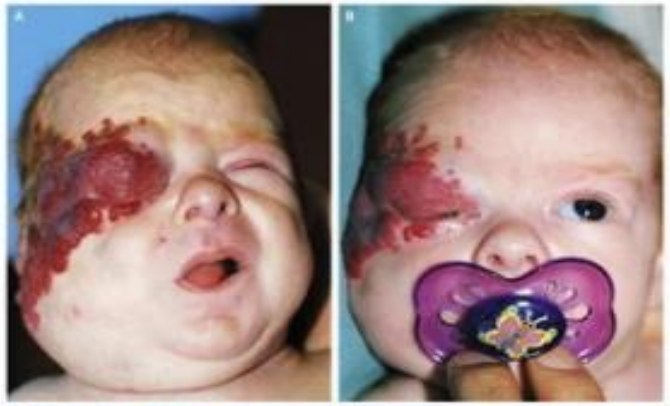
True !

- They simply report a clinical fact, but are sometimes the origin of major therapeutic advances, that may be:
  - the result of chance…
  - or driven by a pathophysiological process

Propranolol for severe hemangiomas of infancy.

Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, et al. N Engl J Med. 2008 Jun 12;358(24):2649-51

- The child had a facial capillary **hemangioma**.
- Due to corticosteroids, the patient developed arterial hypertension and cardiopathy
- Subsequently, he was treated with propranolol (beta blocker)



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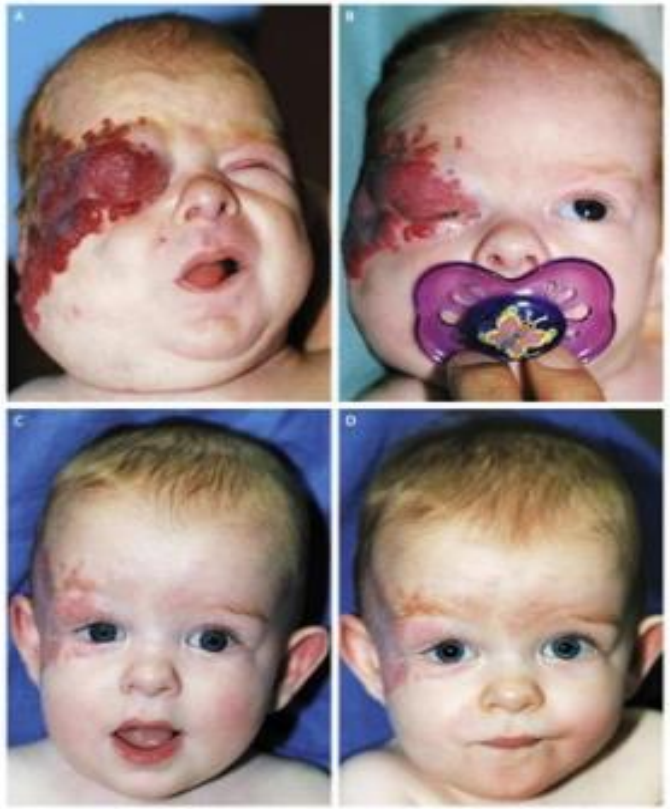
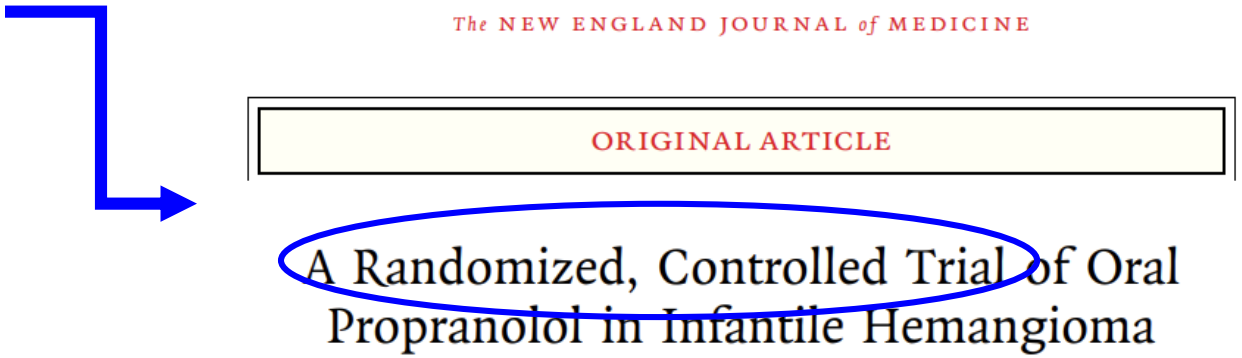


Photographs of Patient 2 before and after Treatment with Propranolol.

- Approval of the drug was then supported by a phase 3 RCT



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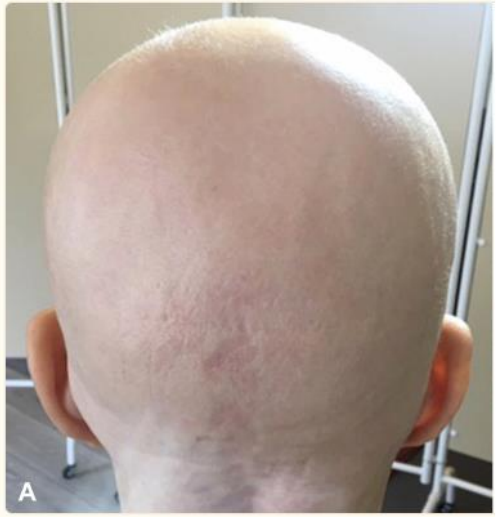
ORIGINAL ARTICLE

A Randomized, Controlled Trial of Oral Propranolol in Infantile Hemangioma

Treatment of severe alopecia areata with baricitinib.

Olamiju B, Friedmann A, King B.JAAD Case Rep. 2019 Oct 22;5(10):892-894

- A woman in her 60s with a medical history of **psoriasis** for which she started treatment with baricitinib (JAK inhibitor).
- She also presented with **alopecia areata** (auto immune disease mediated by a CD8+ T cell infiltrate) resulting in complete hair loss.



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- She also presented with **alopecia areata** (auto immune disease mediated by a CD8+ T cell infiltrate) resulting in complete hair loss.
- After 8 months, she experienced 97% scalp hair regrowth.
- Approval of the drug was then supported by a phase 3 RCT.

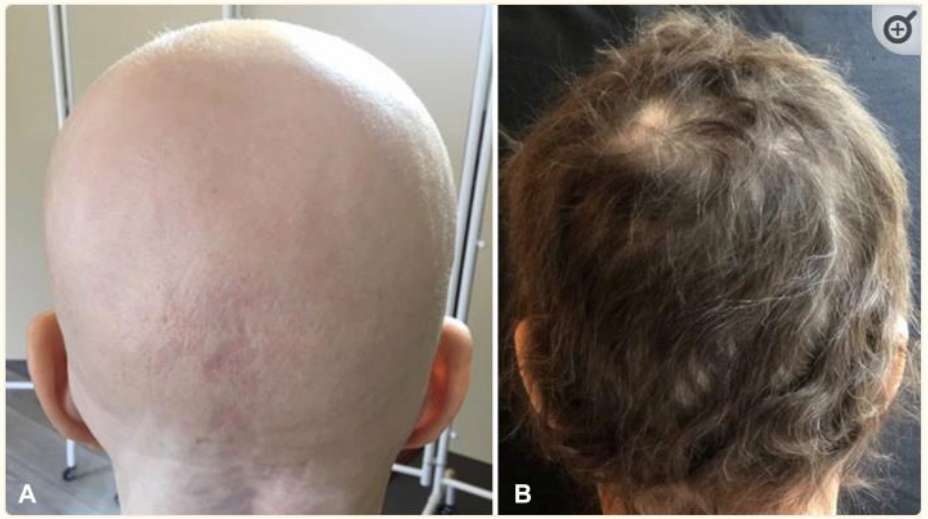


Fig 1

Scalp before and during treatment with baricitinib. **A**, There is no scalp hair before treatment. **B**, After 8 months of daily, there is near-complete scalp hair regrowth.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 5, 2022 VOL. 386 NO. 18

Two Phase 3 Trials of Baricitinib for Alopecia Areata

Brett King, M.D., Ph.D., Manabu Ohyama, M.D., Ph.D., Ohsang Kwon, M.D., Ph.D., Abraham Zlotogorski, M.D., Justin Ko, M.D., Natasha A. Mesinkovska, M.D., Ph.D., Maria Hordinsky, M.D., Yves Dutronc, M.D., Wen-Shuo Wu, M.D., Jill McCollam, Pharm.D., Chiara Chiasserini, Sc.D., Guanglei Yu, Ph.D., Sarah Stanley, Ph.D., Katrin Holzwarth, M.D., Amy M. DeLozier, M.P.H., and Rodney Sinclair, M.D., for the BRAVE-AA Investigators*

Retrospective series / case reports

- Usually report **the off-label use of drugs already marketed in another indication**
- Main issues of retrospective series:
  - Heterogeneous population (different stage, different disease subtypes)
  - Different therapeutic regimen (drug used alone or in combination, various doses)
  - Usually largely over estimate therapeutic results
- Nevertheless, they provide a rationale for conducting a RCT

Phase 1 clinical trials

- Rarely published
- Assess the clinical and biological safety of different doses of the drugs
- Performed in healthy subjects in specialized centers
- Usually combined with pharmacokinetic studies

- Phase 1/2 trials: mainly performed in oncology
- Patients without any therapeutic resource

- Include : drug ranging regimens
  safety assessment
  but also record of preliminary efficacy data

Phase 2 trials

- Extremely important for pharmaceutical companies since they lead to decision to stop or continue the development of drugs (GO / NO GO)

- Usually performed on a limited population of patients, *i.e*. few dozens (phase 2a) to 200 patients (phase 2b)

- **3 main goals**
  - to assess the potential efficacy of a drug in a disease (phase 2a)
    → open studies or sometimes blind RCT versus placebo,
    even if the limited population will likely not allow to reach statistical significance
  - to further assess the safety and first active dose (dose ranging)
  - to provide a strong rationale for a future large phase 3 RCT → blind, versus placebo

Phase 2 trials

- **Interpretation of these trials** (especially early phase2) **is crucial**, as they have significant implications for the drug development process and financial risk…

- **Main issues of phase 2 trials** are related to
  - limited population,
  - especially in case of open studies (absence of control arm),
  - need to rapidly assess the drug efficacy in various potential indications +++

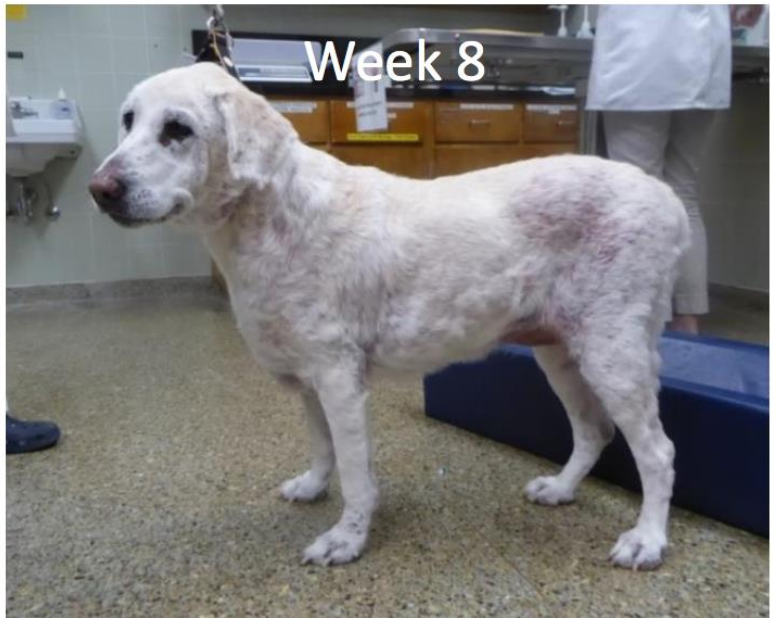
- Difficulties are even higher when the drug efficacy cannot be assessed alone (needs to be combined with another effective drug in acute severe diseases)
- Phase 2b are RCT performed on a larger population, allowing to reach statistical significance and be confident in the results for designing f future phase 3 studies

PRN1008/rilzabrutinib (Bruton Tyrosine kinase inhibitor)

as an example of misinterpretation of the results of a phase 2 trial

Model of spontaneous canine pemphigus :

improvement in 4/4 dogs upon monotherapy with PRN473



Poster 3530, AAD, Washington DC, 2016

Goodale EC et al. Vet Dermatol 2020; 31 : 410-e110

Rilzabrutinib in pemphigus

Phase 2 study in humans:

- 27 patients

- Primary outcome: control of disease activity at Week 4 with low dose of prednisone ≤0,5 mg/kg/d (N=27): 52%

- Issue : the proportion of disease control with this suboptimal dose of CS not exactly known (not a controled trial)

- Clinical remission at Week 12: 22%

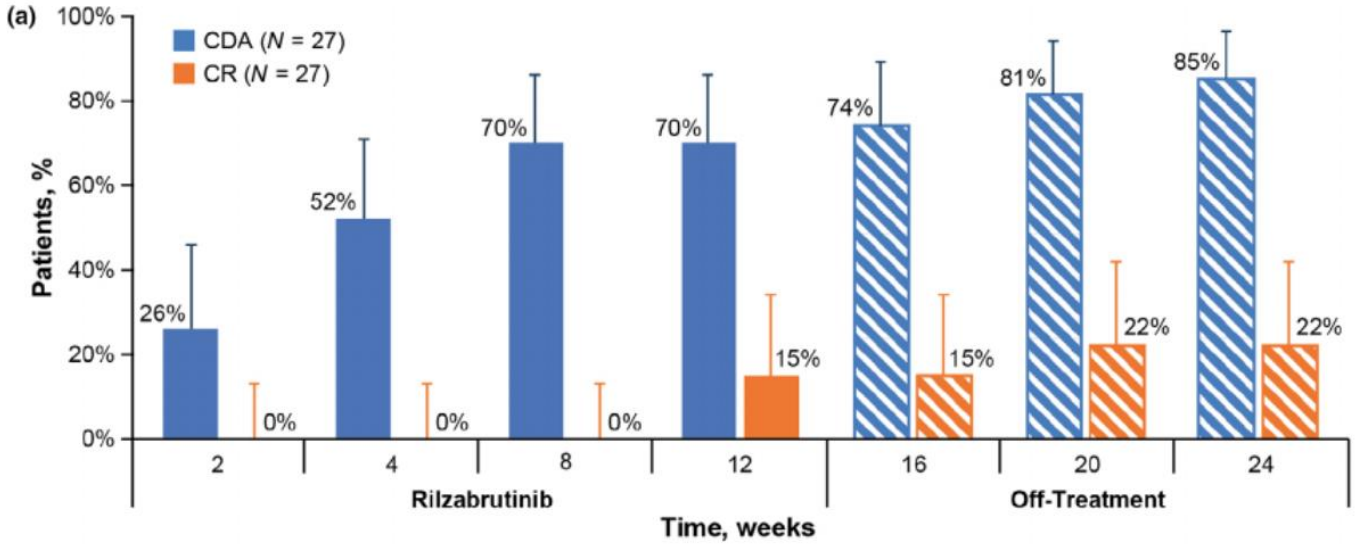
→ suggests a moderate efficacy

CLINICAL TRIAL (2021) 185, pp745–755 BJD British Journal of Dermatology

Proof of concept for the clinical effects of oral rilzabrutinib, the first Bruton tyrosine kinase inhibitor for pemphigus vulgaris: the phase II BELIEVE study

D.F. Murrell,[1] A. Patsatsi,[2] P. Stavropoulos,[3] S. Baum,[4] T. Zeeli,[5] J.S. Kern,[6] A.-V. Roussaki-Schulze,[7] R. Sinclair,[8] I.D. Bassukas,[9] D. Thomas,[10] A. Neale,[10] P. Arora,[10] F. Caux,[11] V.P. Werth,[12] S.G. Gourlay[10] and P. Joly[13] on behalf of the BELIEVE trial investigators

control of disease activity (CDA) and complete response (CR)



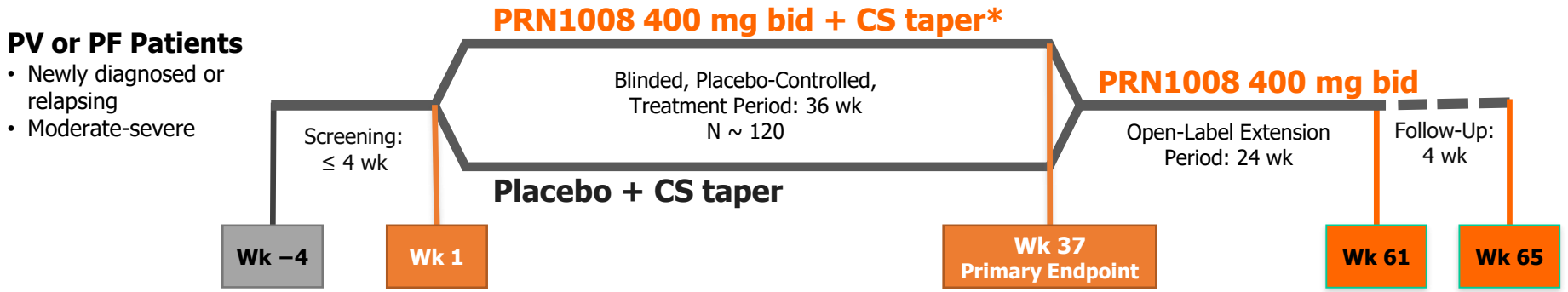
Company organized press releases → drug sold by Principia to Sanofi

Rilzabrutinib in pemphigus

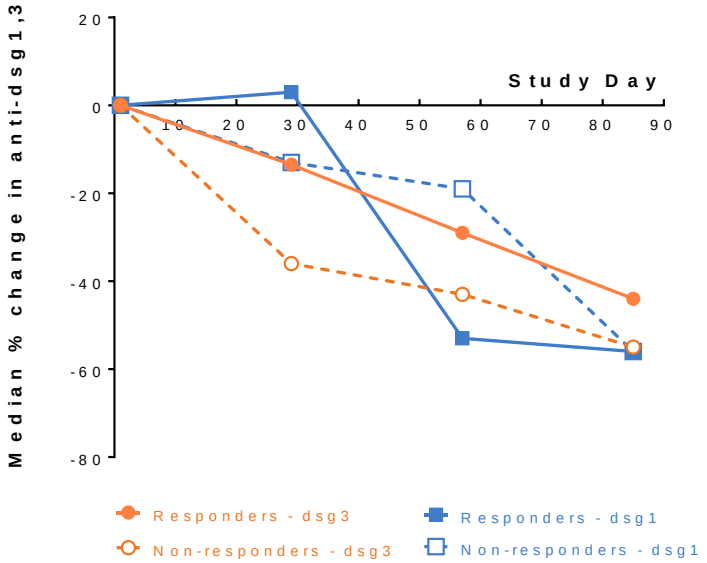
Phase 3 study PEGASUS:

- 120 patients with PV or PF, 19 countries
- Start date: 01/2019, End of inclusions: 09/2020

- Primary outcome: % patients in CR between W29 and W37 with prednisone ≤10 mg/d 26% vs 18% NS



Rilzabrutinib in pemphigus



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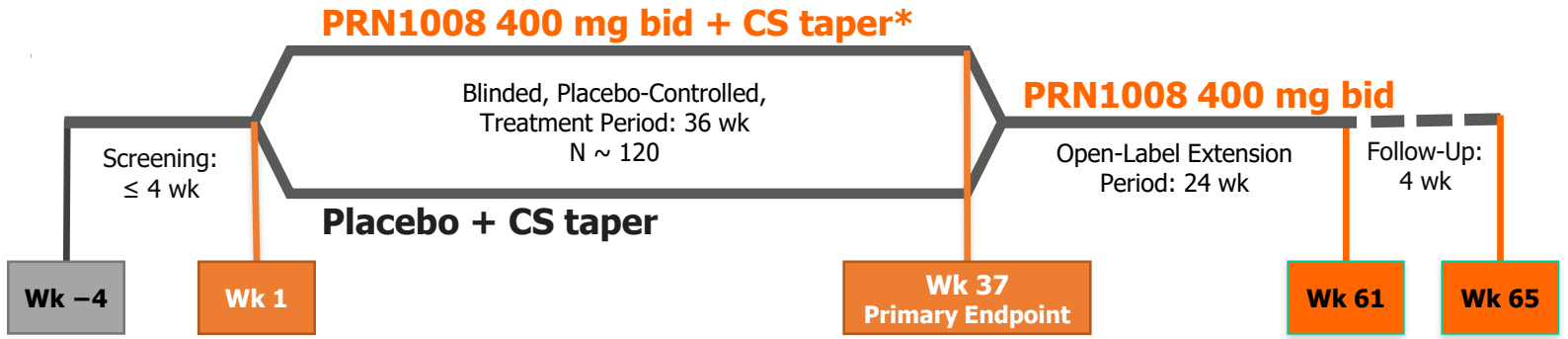


SANOFI

September 09 2021 • PRESS RELEASES

Sanofi provides update on Phase 3 study evaluating rilzabrutinib for the treatment of pemphigus

PARIS – September 9, 2021 – The Phase 3 PEGASUS trial evaluating rilzabrutinib to treat pemphigus, a rare autoimmune skin condition, did not meet its primary or key secondary endpoints. Rilzabrutinib's safety profile remained consistent with previous results and no new safety signals were identified.

Phase 2 trials

- Given the importance of these phase 2 trials ,
  the potential difficulties in interpreting their results,
  their potential financial implication related to the very high cost of phase 3 trials,

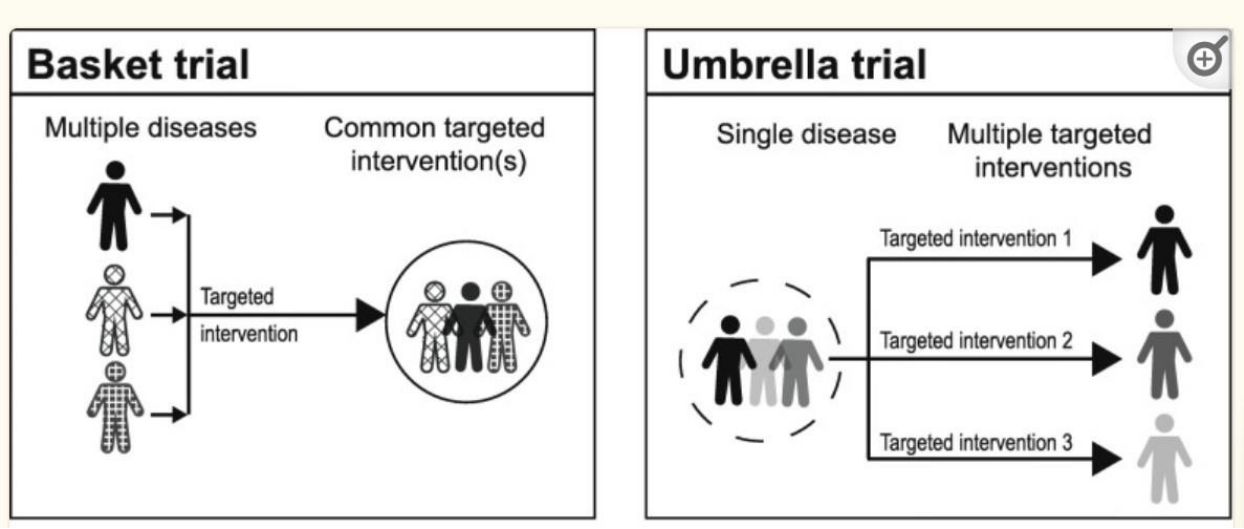
- Some procedures have been developed to solve these issues, to gain time, to have a greater flexibility: **Master protocols and Adaptive trials**

- The term "**Master protocol**" refers to a single design developed to evaluate multiple hypotheses under a common infrastructure, which most often needs that the protocol is differentiated into multiple parallel sub-studies
- Masters protocol are classified into "**basket trials", "umbrella trials", and "platform trials**

- In **Adaptive trials,** patient outcomes are observed and analyzed at predefined interim points and predetermined modifications to study design can be implemented based on these observations.

Master protocols

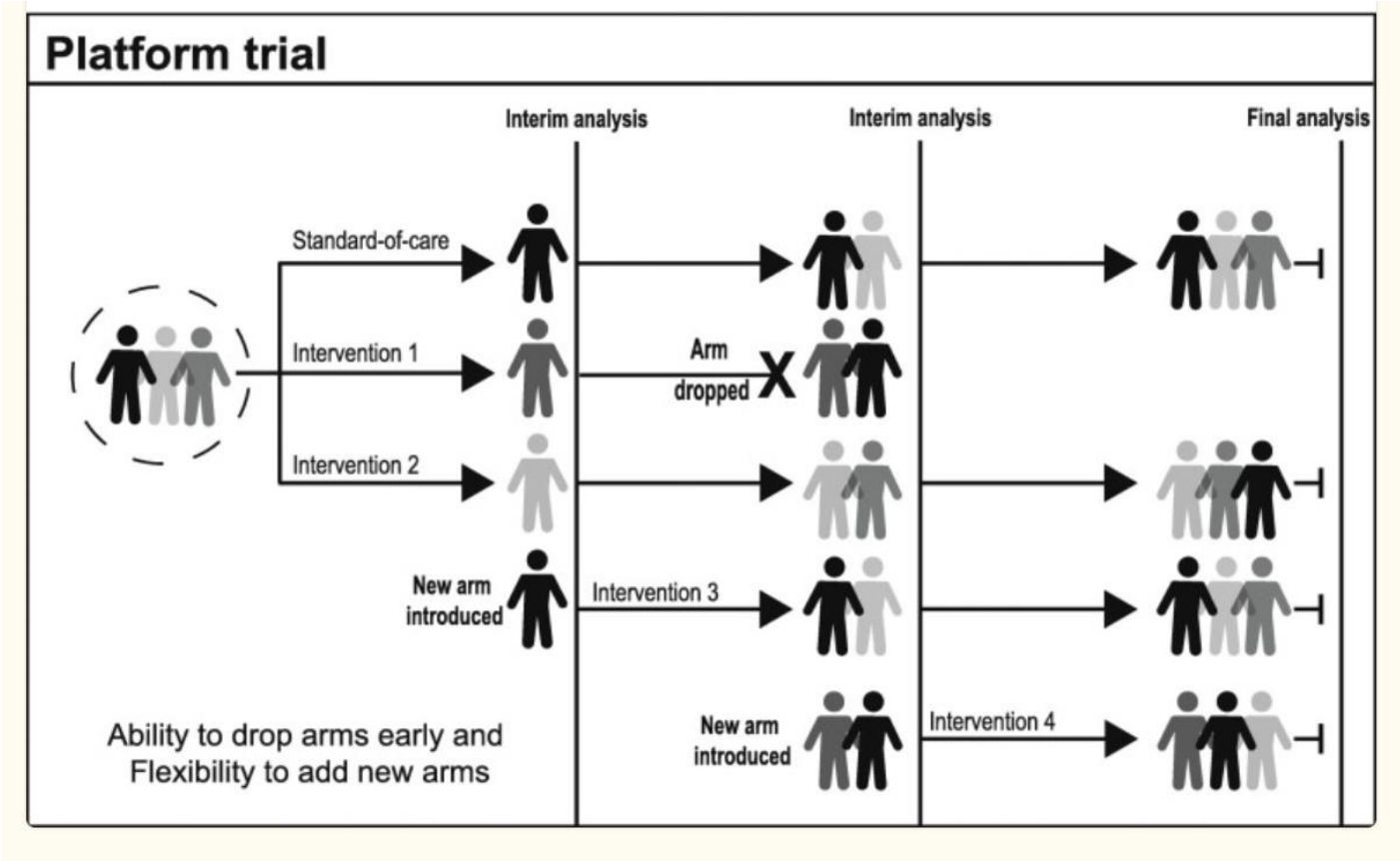
- **Basket trials** refer to designs in which a targeted therapy is evaluated on multiple diseases that have common molecular alternations.
- Ex: Jak inhibitors in alopecia areata, vitiligo, atopic dermatitis…



- **Umbrella trials** evaluate multiple therapies for a single disease which may be stratified into subgroups
  - by molecular alteration in case of tumors with multiple genetic mutations
  - by metabolic pathways/ cytokines involved in inflammatory/ auto immune diseases .
  - by stage / disease severity
- median number of interventions investigated in umbrella trials in the literature is 5

Adaptive trials

- **Adaptive trials** evaluate several interventions against a common control group.
- This design has **pre-specified** adaptation rules to allow dropping of ineffective intervention(s) and flexibility of adding new intervention(s) during the trial
- Adaptive designs offer the benefit of **flexibility** to update trial design and objectives as data accrue.



Most frequent types of adaptation

- **Dose selection**
- **Sample size re-assessment**
- **Dropping an arm**
- **Bayesian adaptive randomization**
  the randomization is adapted during the trial based on the results of interim analyses
  (allows the reassessment of initial statistical hypothesis and adaptation of the design based on new hypothesis)
- **Stopping-for-futility analysis**
  (there is no longer any chance to demonstrate a statistically significant difference between treatment groups)
- **Stopping early for efficacy**
  (to limit the risk of exaggerate benefit, an alpha error rate at 0.005 is generally recommended)

Phase 3 trials

- Large RCTs, potentially leading to market authorization
- Mostly industry-sponsored

- **Superiority trial** +++ (more rarely, non-inferiority studies)
- Most often **double blind**

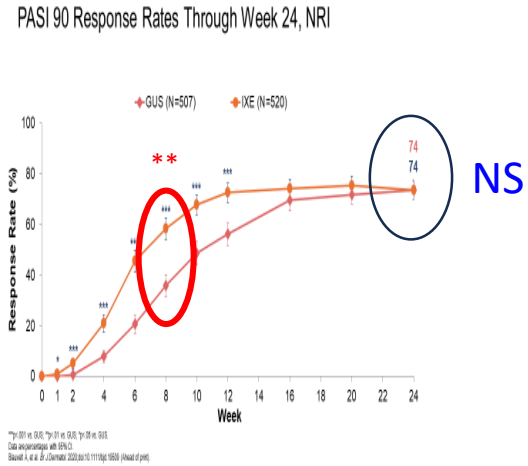
- Always need large fundings
- Supported by the results of phase 2 trials

- Design **against placebo or validated active comparator** (standard of care)
- Usually 2 arms, more rarely 3 arms

- **Homogeneous population of patients** selected on inclusion and exclusion criteria

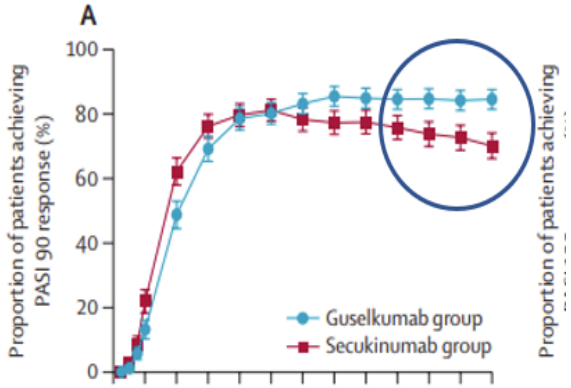
Phase 3 trials: Primary end point

- Interpretation of results are based on assessment of the **primary endpoint**
  - must provide a high chance to reach statistically significance
  - chosen to evidence the advantage of the tested drug relative to comparator



NS

Head to head comparison of anti-IL-17 vs anti-IL-23 in psoriasis



rapidly effective drug= early end point

persistent activity = late endpoint

- clinically significant (biological parameters are only used as secondary end points)
- calculation of the number of patients : **power** is the probability that the study will detect a true effect if it exists, it is typically expressed as a percentage (e.g., 80% power) and is calculated before the trial based on the expected inter group difference

Phase 3 trials: Secondary endpoints

- Aim to describe the various interests of the drug:
  - delay of action,
  - persistence of clinical activity under treatment or after treatment withdrawal,
  - relapse rate, delay of relapse
  - severe and non-severe adverse events
  - quality of life, and patients reported outcomes (pruritus, sleep disturbance…)

- Agencies often recommend **ranked secondary endpoints**: prioritization of the secondary end points depending on their clinical relevance:
  - the first secondary endpoints analyzed is the one which has the highest clinical relevance
  - the second secondary endpoint is analyzed only if the first secondary end point is positive etc ….

- may include **exploratory endpoints:** evolution of immunological parameters/ transcriptomic analyses…

Example of phase 2 leading to a phase 3 trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Single Cycle of Rituximab
for the Treatment of Severe Pemphigus

Pascal Joly, M.D., Ph.D., Hugo Mouquet, Ph.D., Jean-Claude Roujeau, M.D.,

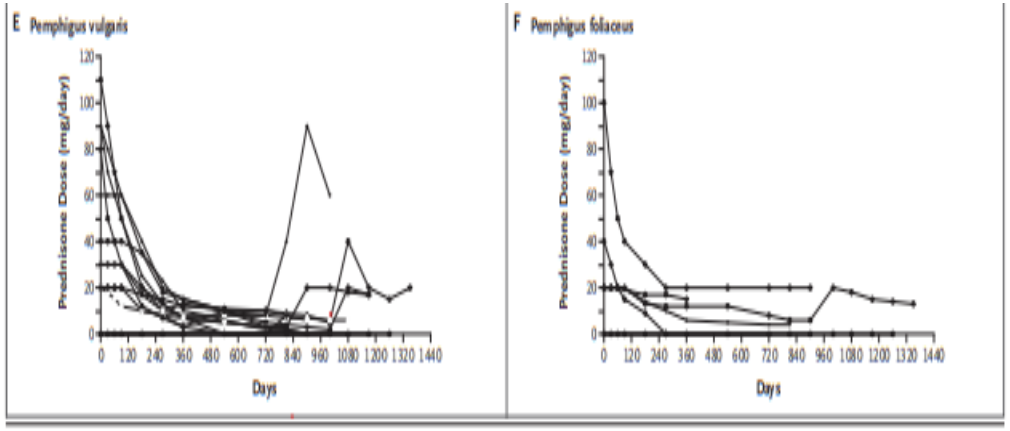
THELANCET-D-16-06623R2
S0140-6736(17)30070-3
Embargo: [add date when known]

16TL6623
Articles
PV

First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial

Pascal Joly, Maud Maho-Vaillant, Catherine Prost-Squarcioni, Vivien Hebert, Estelle Houivet, Sébastien Calbo, Frédérique Caillot,

- open non randomized phase 2 clinical trial
- 21 patients with severe type of pemphigus (AI disease mediated by anti-Dsg Abs)
- treated with rituximab (anti-CD20 mAb)
- spectacular results 18 of 21 patients **(86%) had a complete remission**



- Academic RCT comparing rituximab with a standard oral CS regimen (standard of care)
- Primary endpoint CR off corticosteroids
- Limited population (90 patients) based on the high efficacy demonstrated in the phase 2 trial

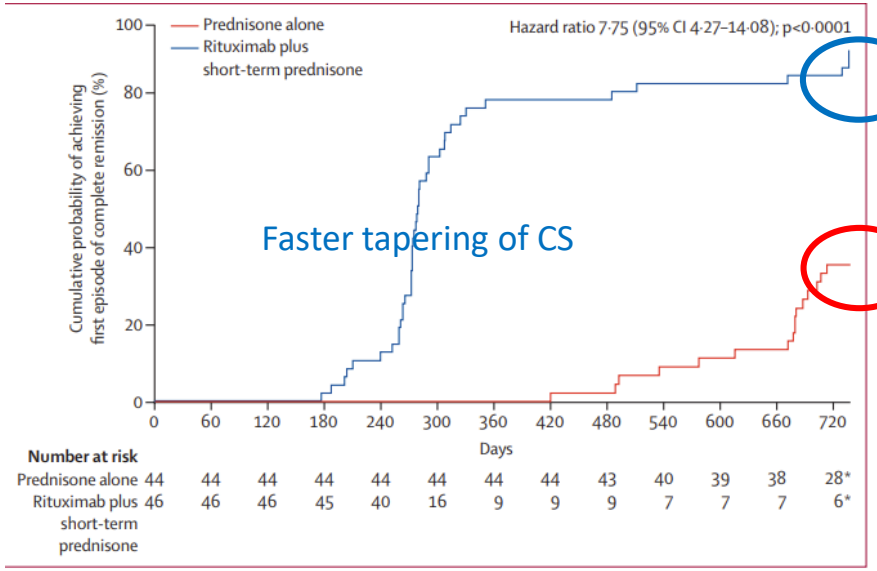


Figure 2: Cumulative probability of achieving complete remission off-therapy.

→ Approval of rituximab in pemphigus by FDA and EMA

Phase 4 studies

- Whereas phase 3 studies are designed to demonstrate the efficacy of a drug, **phase 4 studies** test already marketed drugs with the aim to compare different **treatment strategies** to **define the optimal use of the drug in real-world use**

- These treatment strategies may be based on:

  - chronology of treatment (isotretinoin as first line versus second line in acne)

  - use of combination of drugs (anti PD1+ anti-CTLA 4 vs anti-PD1 in metastatic melanoma)

  - use of biomarkers… to predict treatment response:

    to predict the prognosis and adapt therapeutic strategy (LDH in lymphoma)

    to predict relapse an re-treat patients to avoid relapses (acute leukemia)

What is the protocol of a clinical trial?

- The clinical trial protocol is the central blueprint that defines every aspect of a trial's design, conduct, analysis, and reporting.
- A protocol specifies the trial's rationale, objectives, design, methodology, participant criteria, interventions, endpoints, statistical analyses, and ethical safeguards
- A protocol must be complete, unambiguous, and aligned with quality-by-design principles.

Conclusion

- Identification of molecular abnormalities, gene mutations, immunological pathways provides major rationale for targeting the identified biological abnormalities with new therapeutic agents

- Large phase 3 double blind RCTs remain the gold standard for regulatory agencies to minimize biases in the assessment of drugs and get approval

- Master protocols and adaptive trials are increasingly used despite their methodological complexity to allow a greater flexibility, and to save time and money

- The clinical trial protocol defines every aspect of a trial's design, conduct, analysis, and reporting.

Some specialized references on advanced clinical trial methodology

- Adaptive Designs for Clinical Trials
  Bhatt DL, Mehta C. **N Engl J Med**. 2016; 375(1):65-74. doi: 10.1056/NEJMra1510061

- Adaptive design clinical trials: a review of the literature and ClinicalTrials.gov.
  Bothwell LE, Avorn J, Khan NF, Kesselheim AS. **BMJ** Open. 2018;8(2):e018320

- Changing platforms without stopping the train: experiences of data management and data management systems when adapting platform protocols by adding and closing comparisons
  Dominic Hague, Stephen Townsend, Lindsey Masters, et al. **Trials**. 2019; 20:294. doi: 10.1186/s13063-019-3322-7

- Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols
  Jay J. H Park, Ellie Siden, Michael J. Zoratti, et al. **Trials**. 2019; 20:572. doi: 10.1186/s13063-019-3664-1

- Practical guidance for running late-phase platform protocols for clinical trials: lessons from experienced UK clinical trials units
  Sharon B. Love, Fay Cafferty, Claire Snowdon, et al. **Trials**. 2022; 23:757. doi: 10.1186/s13063-022-06680-4

- Bayesian statistics for clinical research
  Ewan C Goligher, Anna Heath, Michael O Harhay. **Lancet** 2024; 404(10457):1067-1076. doi: 10.1016/S0140-6736(24)01295-9

Designing a clinical trial protocol

(A simplified protocol is given to participants as an example)

What should the protocol of a clinical trial contain?

Title Page & Approvals	Protocol title (often includes disease/population and study acronym), identifying number, versions (dates) of protocol and any amendments, signatures of sponsor and investigators.
Synopsis	A concise summary of the trial design, objectives, key eligibility criteria, treatments, endpoints, and schedule.
Introduction / Background	Scientific rationale and context including relevant preclinical and clinical data on the intervention(s). This section justifies why the study is needed.
Objectives / Purpose	Clear statement of primary and secondary objectives (what questions the trial aims to answer).
Endpoints / Outcomes	Definition of primary, secondary, and exploratory endpoints (efficacy and safety outcomes), specifying how each will be measured and assessed.
Trial Design	Detailed description of overall design (e.g. randomized controlled trial, factorial, crossover, open/closed label). Includes randomization method, blinding (who is blinded), number of arms/treatment groups, and a schematic diagram of trial flow.
Population / Eligibility	Inclusion and exclusion criteria delineating who can or cannot participate.
Withdrawal/Discontinuation	Criteria and procedures for when/how to withdraw subjects (e.g. adverse events, pregnancy, noncompliance).
Interventions / Treatments	Description of the investigational product(s) and control(s): dosing (amount, schedule, route), formulation, administration procedures, and comparator details. Includes any permitted or prohibited medications.

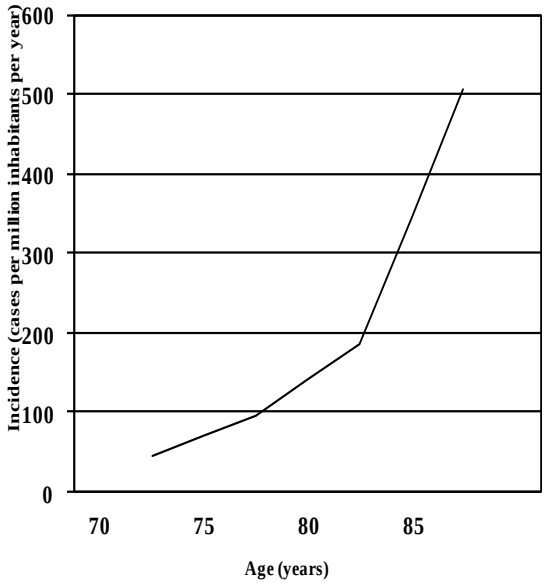
What should the protocol of a clinical trial contain?

Study Visit Schedule	Timeline of study periods (screening, treatment, follow-ups), with schedule of planned assessments (e.g. baseline, each visit). Often presented as a table.
Assessments / Data Collection	What data will be collected, when, and how. Mechanisms for data recording and handling.
Efficacy Assessment and Analysis	Statistical analysis plan: describes statistical methods, handling of missing data, interim analyses, criteria for stopping trial (if any). Specifies sample size calculation (with assumptions for effect size and power) and planned population for analysis (e.g. intent-to-treat).
Safety Assessment	Definitions of adverse events (AEs) and serious AEs, procedures for AE reporting, and follow-up.
Data Handling & Record Keeping	Describes how data are recorded, codes, case report forms, electronic CRFs, database, retention policies, and who has ownership of data.
Quality Assurance / Monitoring	An outline of quality control and assurance activities.
Ethical Considerations	Confirmation that the trial will be conducted in compliance with GCP and ethical principles, description of IRB/IEC processes, informed consent procedures, confidentiality protections.
Financing and Insurance	Funding sources, compensation to investigators or subjects, and insurance against trial-related injury, if applicable.

Building a phase III clinical trial through an example

- One disease : bullous pemphigoid
- One candidate therapy : omalizumab

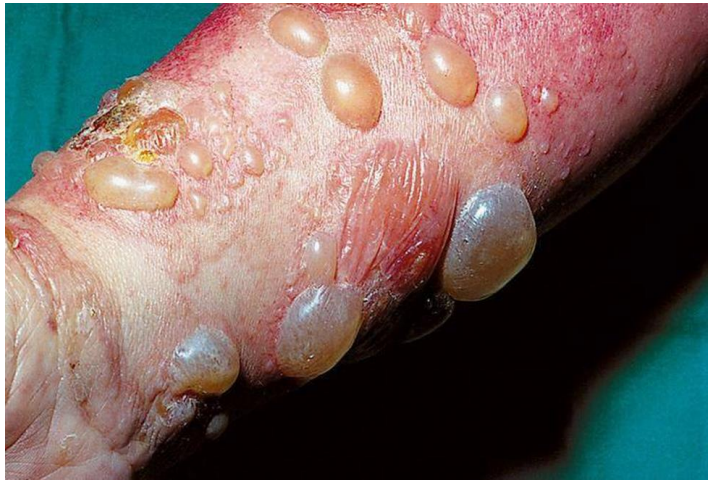
Background in bullous pemphigoid



= most common AIBD and increasing incidence

Elderly patients (mean age = 80 years)
with **neurological comorbidities** (40%)

Initial symptom: pruritus
Tense blisters on erythematous or urticarial skin
Leading to large erosions



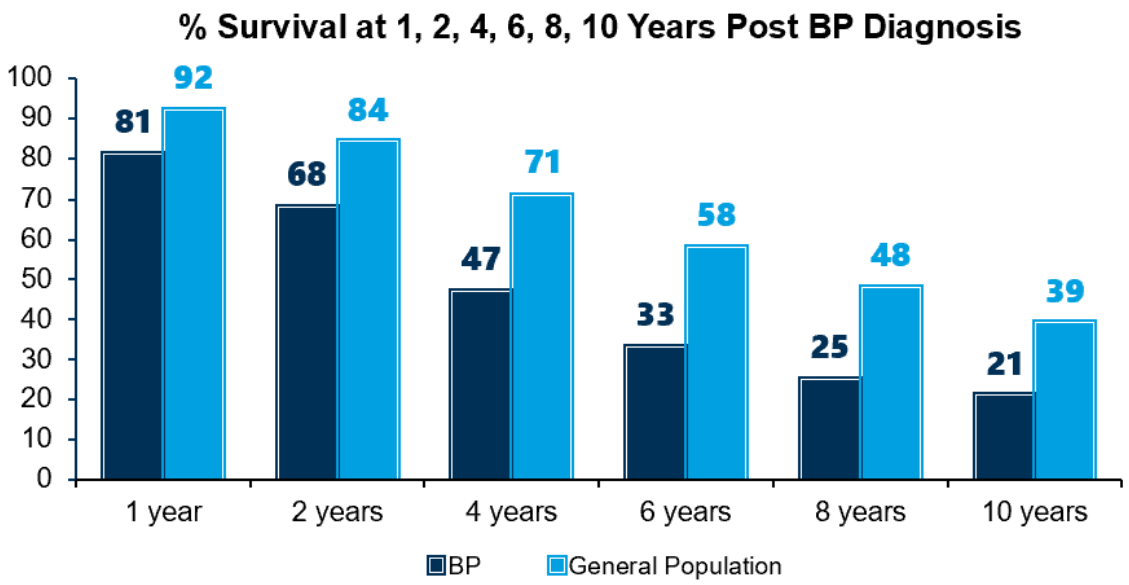
Rare mucosal lesions: 10-20%, mostly in the oral cavity

Overall: frequent and severe disease in old and fragile patients

Background in bullous pemphigoid

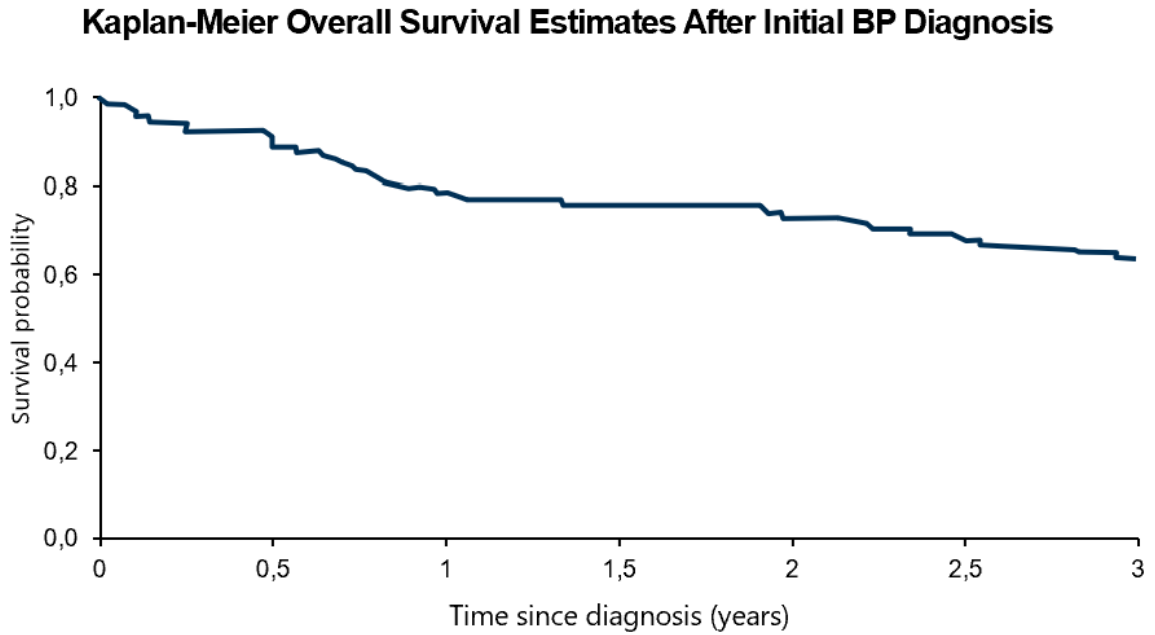
Lower Overall Survival in BP

In a retrospective analysis of 87 BP patients over 10 years, BP was associated with a lower survival rate versus the general population[1]

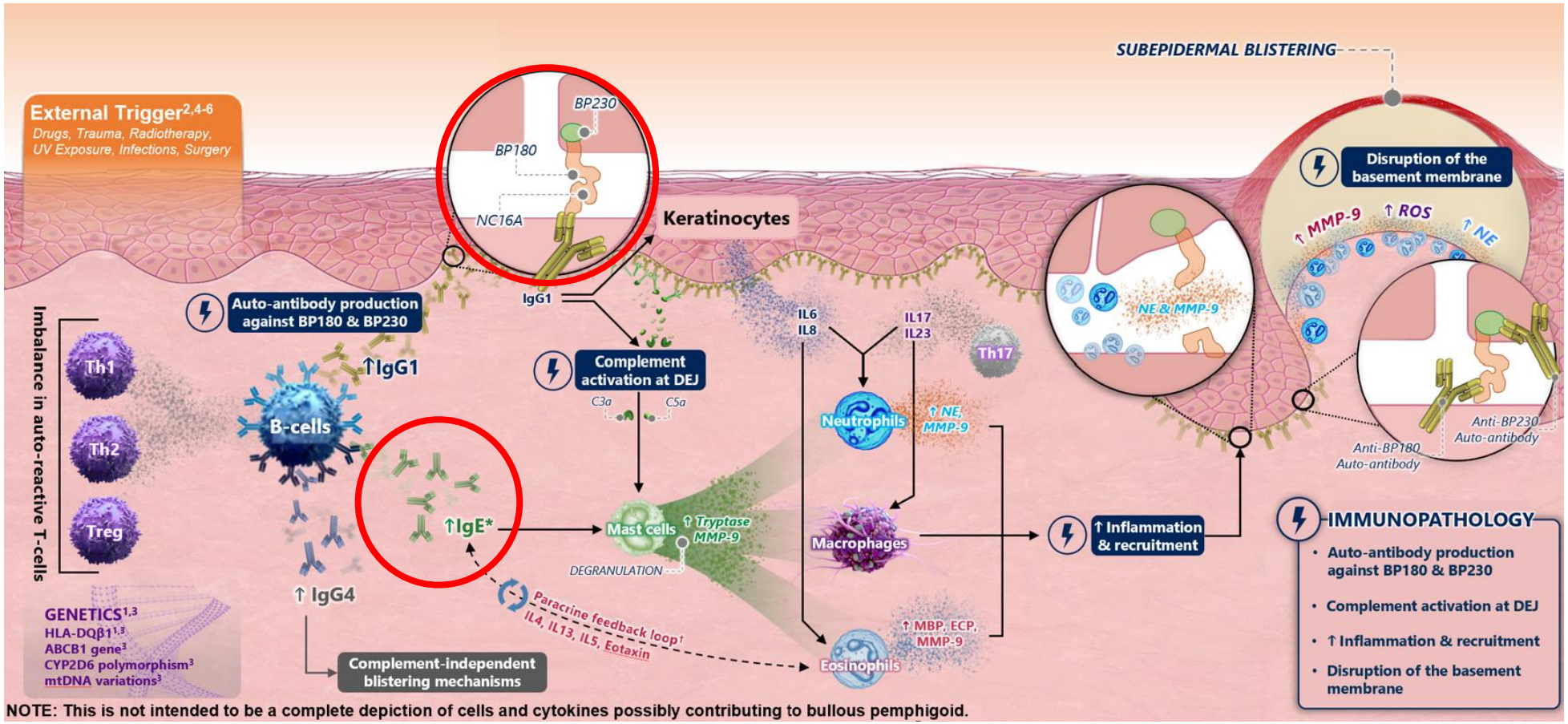


Poor Prognosis in BP

In a prospective cohort of 115 patients followed over 3 years, the **1-**, **2-** and **3-year probability of death** following a BP diagnosis was found to be **20.9%**, **28%** and **38.8%**, respectively[2*]



Involvement of IgE in BP pathophysiology



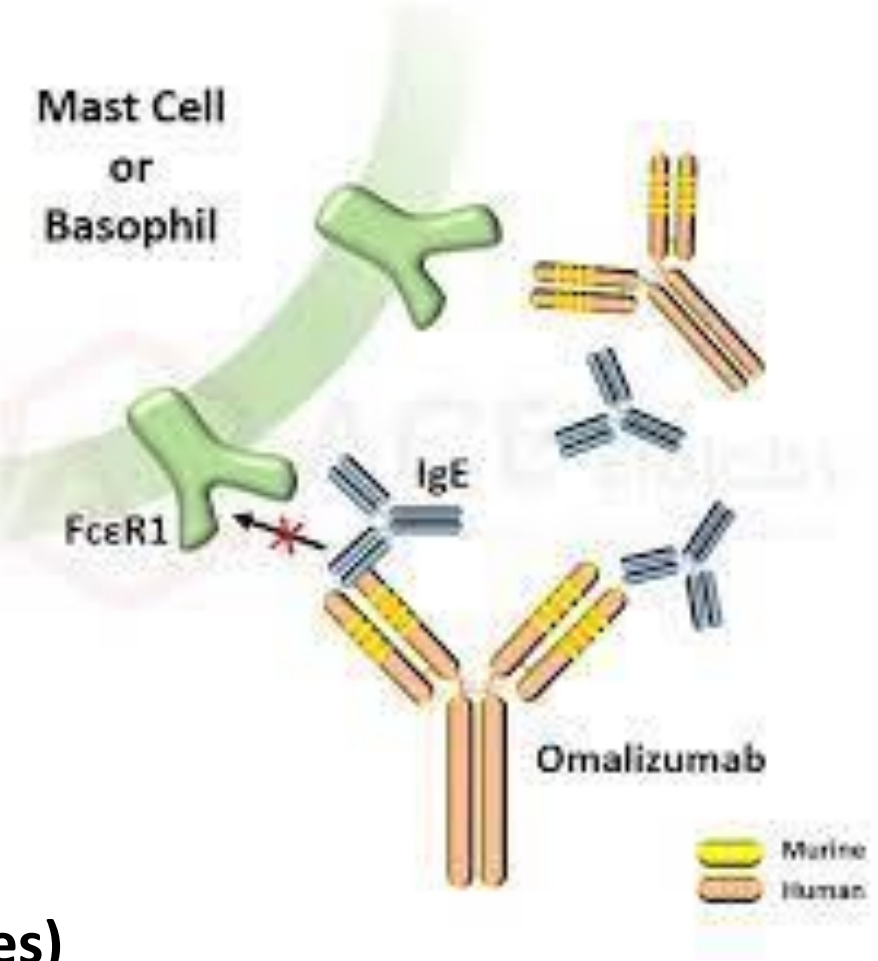
- **Autoantibodies bind to** the NC16A domain of **BP180 (>90%).**
- IgG are mainly **IgG1** but the presence of **IgE** has also been evidenced and even correlated with disease activity.

Treatment recommendations in BP

MILD (BPDAI ≤19)	MODERATE (BPDAI 20–56)	SEVERE (BPDAI ≥ 57)
Topical corticosteroids +++		
In relapsing BP: NO CONSENSUS		
	+/- Systemic steroids	
	+/- Antibiotics	
	+/- Immunosuppressants or immunomodulators	

(Specific treatment recommendations may vary widely among countries)

Background on omalizumab



Anti-IgE monoclonal Ab

Binds to circulating IgE and inhibits the binding of IgE on their receptor on **mast cells**

Limitation of mast cells degranulation and therefore inflammatory cells tissue-recruitment (Eo, PMN, macrophages)

Labelled for **spontaneous chronic urticaria** for many years

Very well tolerated: no specific contraindications

Rationale for omalizumab in BP

1. Patients with Bullous Pemphigoid (BP) are **old and fragile patients** with numerous comorbidities.
2. Topical CS are very effective in the acute phase of BP but **not convenient as maintenance therapy** because of side effects and the need for nursing care frequently responsible for poor compliance and relapses.
3. **Immunosuppressants are poorly tolerated** and therefore weakly used
4. There is a high need for an effective, and **well-tolerated maintenance therapy** that would allow to stop topical CS quite rapidly, while preventing relapses.
5. **Numerous case-series reporting the efficacy of omalizumab**
6. Clinical rationale: **urticarial lesions**
7. Immunological rationale: **anti-BP180 IgE level correlate with BP activity**

Determining objectives and endpoints

What is our main objective ?

Main objective:

To demonstrate that omalizumab (300mg monthly) **is superior to placebo to prevent the occurrence of deaths/relapses, after achievement of complete remission with an initial short term topical corticosteroids therapy with clobetasol propionate cream** (applied for 3 months).

Determining objectives and endpoints

Primary endpoint:

= The main result measured at the end of a study to see if a treatment works
(e.g., the number of deaths or the difference in survival between the treatment group and the control group).

- It is the endpoint for which the trial is powered
- Must be is decided before the study begins +++
- **Must correspond to the main objective +++**

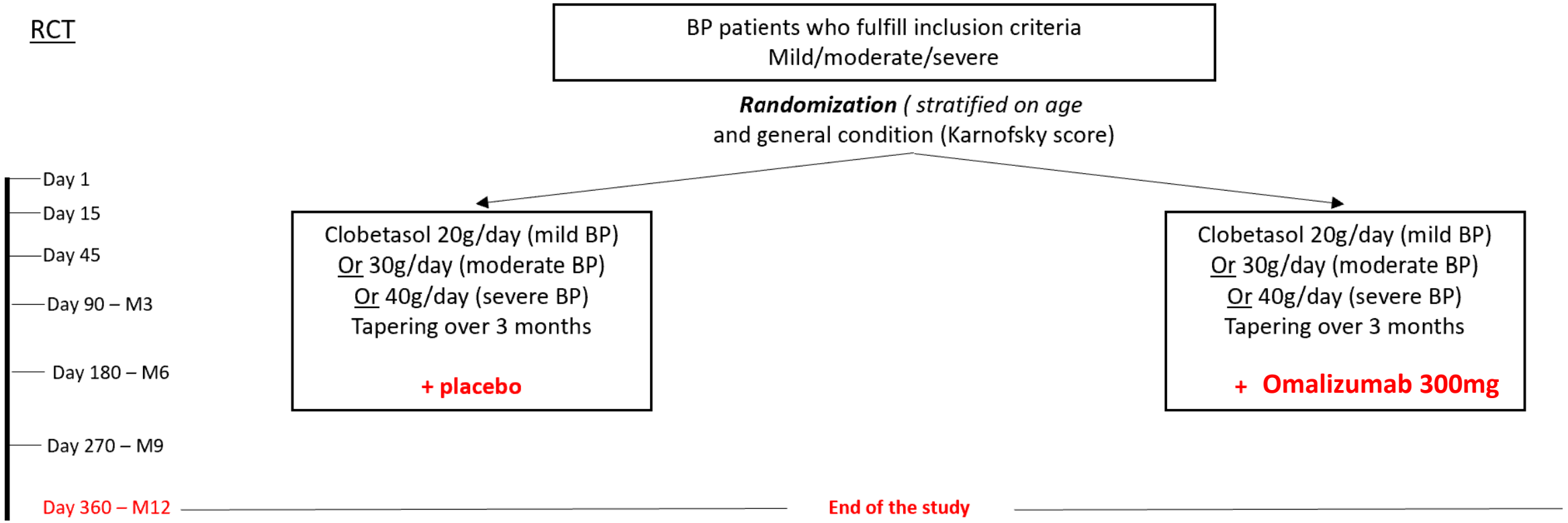
So what would you choose as primary endpoint ?

Determining objectives and endpoints

- **Primary endpoint:**

One-year disease free survival (DFS) off topical corticosteroids measured from the time at which topical corticosteroids are stopped to the first relapse or until Month 12 in patients who maintain sustained CR.

Study design



Determining objectives and endpoints

Secondary objective

= what are other important questions ?

Secondary endpoints

Must correspond to each secondary objective

Secondary objectives and corresponding endpoints

Secondary objective

1. To assess the number of relapses occurring on omalizumab or placebo according to the initial severity of BP (mild moderate, severe) as assessed by the BPDAI score
2. To compare the durability of remission on ligelizumab and placebo according to the initial severity of BP
3. To describe the number and distribution of rescue therapies
4. To compare the effects of omalizumab and placebo on patients' quality of life (QoL)
5. To compare the 12-months overall survival of patients on maintenance therapy with omalizumab and placebo
6. To compare the safety of omalizumab and placebo

Secondary endpoints

1. DFS according to BP initial severity (mild, moderate, severe) as assessed by the BPDAI score
2. Delay of relapse, from the date of CR off topical CS, according to BP initial severity (mild, moderate, severe)
3. Number and distribution of rescue therapies
4. Evolution of QoL scores (ABQOL**)**
5. One-year overall survival rate
6. Mean number of adverse events (AE) and severe adverse events (SAE) (including death) per patient and per month of treatment exposure

Inclusion criteria

Definition: **“Inclusion criteria are positive criteria describing the characteristics that people must have in order to be included”**

Inclusion criteria must include:

Age ≥ 18-year-old (except in pediatric research…)

Diagnostic criteria of the concerned disease +++

Patient able to receive the treatment

Patient having read and understood the information letter and signed the Informed Consent Form

In our example:

- **Confirmed newly diagnosis of BP according to:**
  - Clinical features suggestive of BP (at least 3 out of 4 Vaillant clinical criteria for BP: age > 70 yo, absence of mucosal involvement, absence of atrophic scars, absence of predominant involvement of head and neck and the upper side of the trunk
  - subepidermal blister on skin biopsy, or margination of eosinophils along the dermal epidermal junction in non-bullous types of BP
  - linear deposits of IgG and C3 along the basement membrane zone by direct immunofluorescence

Non-inclusion criteria

“Non-inclusion criteria are negative criteria, i.e. they describe characteristics that people must not have in order to be included in the trial”

Classic (and reproducible) criteria :

- Non-consenting patient or patient who cannot be followed regularly
- Evidence of another close disease = diagnostic doubt
- Atypical form of the disease
- Known contraindication to the assessed molecule
- Pregnant or lactating
- Evidence of severe uncontrolled concomitant disease that, in the investigator’s judgment, would preclude patient participation
- Any concomitant condition that required a treatment that could interfere with the results
- Treatment with efficient molecule within few weeks prior to randomization
- Known active and severe systemic infection within 4 weeks prior to screening.
- Currently active alcohol or drug abuse, or history of alcohol or drug abuse within 24 weeks prior to screening
- Major surgery within 4 weeks prior to randomization, excluding diagnostic surgery.
- Person deprived of liberty by an administrative or judiciary decision or person placed under judicial protection, under guardianship or supervision.
- Person participating to another trial

Sample size

The **data analysis strategy and statistical plan** should be clearly established **before the study is initiated**

Consult with a **statistician and/or a methodologist** experienced in RCT data analysis when designing the study

All relevant outcomes to be evaluated are specified before starting the study

Ensure that the most valued outcome is specified as the **primary outcome** to appropriately calculate the sample size

Sample sizes are estimated on the basis of the **expected effect size of the intervention** versus the control **on the primary outcome**

Determining study schedule

- **Inclusion visit**

= baseline

= randomization

- **Follow-up visits**:

Their number depend on your objective, the tested molecule and the usual practice from guidelines of the disease

For example:

<u>omalizumab will be administered at Day 0, D15 and then monthly</u>

- ➢ You need visits at **D15 and D45** (patients can perform the following injections at home)

<u>from the BP guidelines</u>:

- Control disease must be assessed between **D15 and D21**
- Auto-Abs need to be performed every 3 months
- ➢ You need visits at D15 and **every 3 months**

Determining study schedule

	*Screening V1 **Day -15 to D-05**	Baseline V2 **Day 1**	V3 **Day 15**	V4 **Day 45** (± 5 days)	V5 **M3 = Day 90** (± 5 days)	V6 **M6 = Day 180** (± 5 days)	V7 **M9 = Day 270** (± 5 days)	V8 **M12 = Day 365** (± 5 days)
Patient information	✓							
Written informed consent	✓							
Subject demography	✓							
Medical history	✓							
BP History	✓							
Review Inclusion/Exclusion criteria	✓							
Randomization (maximum at Day -10)		✓						
Physical examination	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs, temperature	✓	✓	✓	✓	✓	✓	✓	✓
Laboratory testing blood chemistry, haematology	✓				✓	✓		✓
Additional Screening lab testing serology for HIV, serology for hepatitis B, serology for hepatitis C, sedimentation rate, CRP, serum electrophoresis	✓							
Disease Activity Health Outcomes Assessments: BPDAI score	✓	✓	✓	✓	✓	✓	✓	✓
Quality of life score	✓			✓		✓		
Immunological laboratory testing: serum for ELISA		✓			✓	✓	✓	✓
Omalizumab injection or corresponding SC placebo		✓	✓	✓				
*Omalizumab dispensing or corresponding SC placebo				✓	✓ (3 units)	✓ (3 units)	✓ (3 units)	

Cost estimation

Very important (obviously…)

To obtain fundings of investigator-initiated CT

To have enough funds to achieve the study +++

<u>Will be considered</u>:

Molecule / Placebo price +++
Visits / Consultations / Hospitalizations
Staff: methodologist, statistician, pharmacy
Blood samples
Patients transports
Administration +++
Etc…

Ethical aspects

CTs require approval by an **ethics committee**

Information provided to patients as part of the informed consent process must **clearly describe** what randomization is and must ensure that patients are aware of what allocation to the intervention or control group involves.

- **Signed informed consent form**

Ethics boards may require that the intervention, if found to be beneficial, be offered to patients in the control group at the end of the study, so as to avoid imparting a health advantage to those randomized to the intervention group.

Writing the protocol !!!

Once you have answered to the previous steps,
you have to transcribe it with details:

- Background
- Objective
- Endpoints
- Inclusion / exclusion criteria
- Characteristics of the studied molecules (dosage, pharmacocinetics, pharmacodynamic, toxicity…)
- Protocol details(visits, clinical assessments, biological analyses etc…)
- Feasibility
- Statistical analysis
- Budget

= Around 150 pages of details about that you plan to do….

Take home messages

- ✓ Designing and realize a clinical trial is a long process
- ✓ From the intention letter to the publication of results ≈ 5-7 years
- ✓ You need to be sure that you will be able to complete the study +++ it's always more difficult than planned
- ✓ Define the good question and find the appropriate methodology to answer it are the two main steps

(A simplified protocol is given to participants as an example)