# Suitable Patient Populations and Study Designs for rapid PoC

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# Utilization of patient populations with „monocausal“ diseases – Cryopyrin associated syndrome (CAPS)

- (CAPS) comprises a spectrum of apparently distinct, rare, inherited inflammatory disorders of increasing severity, including the familial cold autoinflammatory syndrome, the Muckle–Wells syndrome, and others. Patients have severe fatigue, fever, and influenza-like myalgia, chronic anemia + inflammation of skin, eyes, bones, joints, meninges.
- Clinical features include rash, conjunctivitis, arthritis, chronic meningitis, sensorineural deafness, and intellectual impairment.
- Systemic AA amyloidosis that causes renal failure and usually results in death within 5 to 10 years develops in approximately 25% of patients
- Interleukin-1β can induce a range of responses, including fever, pain sensitization, bone and cartilage destruction, and the acute-phase plasma protein response. The pivotal pathogenic role ofinterleukin-1 in CAPS has been demonstrated

CAPS study group N Engl J Med 2009;360:2416-25.



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# Treatment with Canakinumab (Anti-IL1beta)

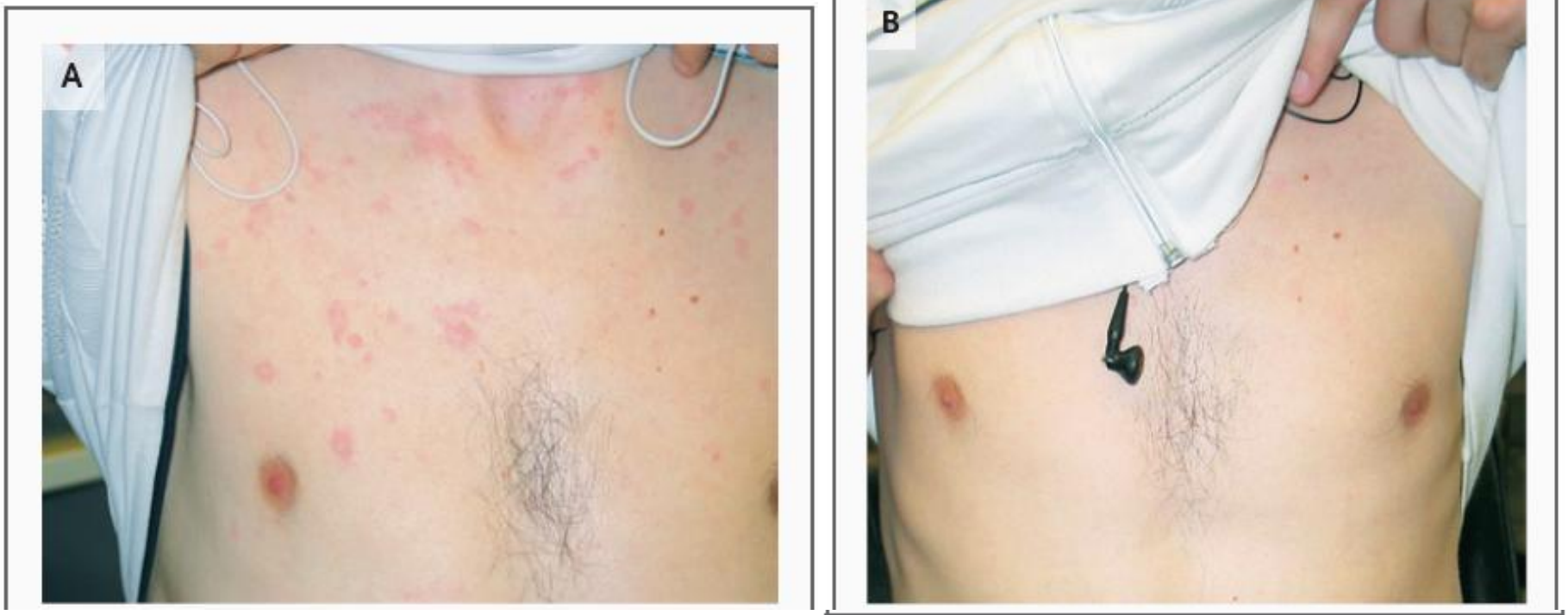


**Figure 1. Response of Rash to Canakinumab in a Patient with the Cryopyrin-Associated Periodic Syndrome (CAPS).**

Immediately before the administration of the initial dose of canakinumab, this patient had a typical urticarial rash (Panel A). Within 24 hours after the administration of a single dose of canakinumab, the rash had almost completely disappeared (Panel B).

CAPS study group N Engl J Med 2009;360:2416-25.

# Aldosterone Synthase Inhibition with LCI699-use in primary disease

**Table 2. Plasma and Urine Hormone Changes Before and After LCI699 in 14 Patients With PA**

| Variables | Placebo, Day −15 | LCI699 Day 1 (Baseline) | LCI699 Day 8 (0.5 mg BID) | LCI699 Day 15 (0.5 mg BID) | LCI699 Day 22 (1.0 mg BID) | LCI699 Day 29 (1.0 mg BID) | Placebo, Day 36 | *P*§ |
|---|---|---|---|---|---|---|---|---|
| Plasma aldosterone, pmol/L | 395 (300 to 520) | 540 (394 to 739) | 173 (131 to 230)* | 171 (128 to 230)* | 132 (100 to 173)* | 133 (100 to 177)* | 400 (315 to 508) | <0.0001 |
| 24-h urine aldosterone excretion, nmol/24 h | 82 (61 to 109) | 93 (70 to 123) | 21 (15 to 29)* | 17 (12 to 24)* | 10 (7 to 15)* | 11 (8 to 15)*† | 71 (54 to 94) | <0.0001 |
| Plasma 11-deoxycorticosterone, pmol/L | 156 (99 to 246) | 170 (107 to 268) | 1373 (1059 to 1779)* | 1723 (1329 to 2234)* | 2968 (2414 to 3648)* | 2590 (2101 to 3193)*‡ | 585 (425 to 804)* | <0.0001 |
| Plasma renin concentration, mUI/L | 10 (7 to 13) | 11 (8 to 15) | 13 (10 to 18) | 14 (11 to 19) | 15 (11 to 19) | 15 (12 to 18) | 12 (9 to 15) | 0.0007 |
| Plasma cortisol, nmol/L | 298 (258 to 345) | 285 (251 to 323) | 307 (273 to 346) | 306 (277 to 339) | 298 (263 to 337) | 272 (232 to 319) | 283 (253 to 316) | 0.73 |
| Plasma 11-deoxycortisol, nmol/L | 1.44 (1.44 to 1.44) | 1.65 (1.38 to 1.96) | 1.94 (1.56 to 2.43) | 3.31 (2.40 to 4.57)* | 6.82 (4.94 to 9.43)* | 6.42 (4.93 to 8.34)*† | 1.62 (1.39 to 1.89) | <0.0001 |
| Plasma ACTH, pmol/L | 5 (3 to 7) | 4 (3 to 6) | 5 (3 to 6) | 6 (4 to 8) | 8 (6 to 12)* | 9 (6 to 12)*‡ | 5 (4 to 6) | <0.0001 |

Data are geometric means (95% CI).
*Data show $P<0.0001$ vs day 1.
†Data show $P<0.001$ vs day 15.
‡Data show $P<0.01$ vs day 15.
§Data show *P* value for global time effect by ANOVA.

*Amar et al. Hypertension 2010, 56:831-838*

Aldosterone synthase inhibitor, LCI699, to 14 patients with primary aldosteronism. After a 2-week placebo run-in, patients received oral LCI699 (0.5 mg BID) for 2 weeks, LCI699 (1.0 mg BID) for 2 weeks, and placebo for 1 week.



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# Utilization of similar disease biology-easier PoC in related disease

**Table 2.** Prevalence of rhinitis in asthmatics and patients with atopic dermatitis

| Diagnosis of rhinitis | Asthma | | |
|---|---|---|---|
| | Present ($n = 164$) | Absent ($n = 161$) | $P$ |
| Physician based | 92.1* | 87.6 | 0.38 |
| Positive nasal challenge | 92.1 | 90.1 | 0.53 |
| Test diagnosis | 84.1 | 87.6 | 0.38 |

*Proportion (%).

Teerehorst et al. Clin Exp. Allerg (2002) 32; p1160



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# Montelukast – effect on bronchial obstruction after allergen challenge

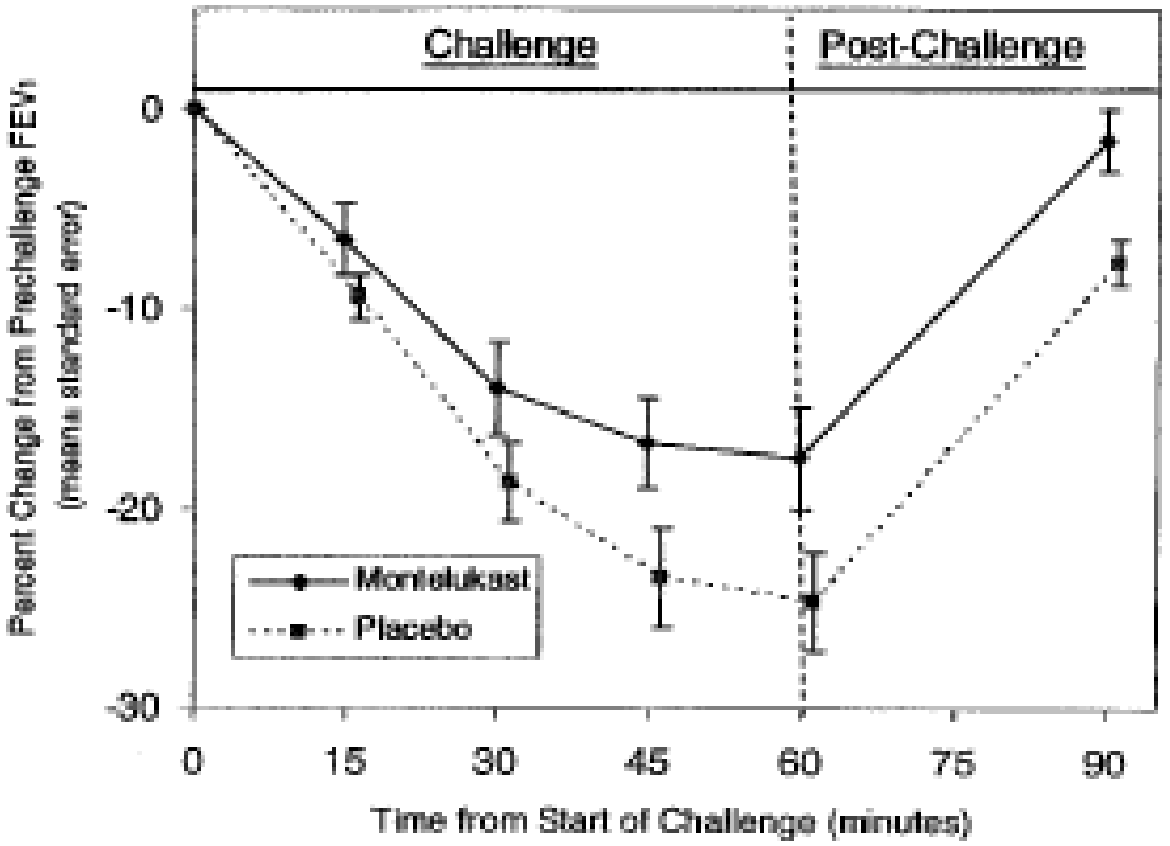


Figure 1. Percentage decrease from prechallenge forced expiratory volume in 1 second ($FEV_1$) during (0 to 60 minutes) and after (60 to 90 minutes) controlled cat allergen challenge.

*Perry et al. Ann Allergy Asthma Immunol. 2004;93:431–438.*



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# Montelukast –allergen challenge; effect on nasal symptoms

Table 4. Change from Prechallenge Nasal Symptoms Score during and after Controlled Cat Allergen Challenge*

| | Challenge period (0–60 minutes) | | Postchallenge period (60–90 minutes) | | Challenge and postchallenge periods combined (0–90 minutes) | |
|---|---|---|---|---|---|---|
| | Mean difference (95% CI) | *P* value | Mean difference (95% CI) | *P* value | Mean difference (95% CI) | *P* value |
| AUC increase in nasal symptoms score, score per hour | −0.11 (−0.25 to 0.03) | .12 | −0.07 (−0.15 to −0.00) | .04 | −0.19 (−0.39 to 0.02) | .07 |

Abbreviations: AUC, area under the curve; CI, confidence interval.

* Differences between montelukast and placebo are shown as least squares mean values, with negative differences favoring montelukast.

*Perry et al. Ann Allergy Asthma Immunol. 2004;93:431–438.*



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# Utilization of Healthy subjects

| | | $E_{max}$ (μU/ml insulin) | $EC_{50}$ (GLP-1 pmol/l) |
|---|---|---|---|
| *Study 1* | | | |
| Mean | | 41.7 | 19.5 |
| SE | | 6.47 | 5.08 |
| Intersubject variability (% CV) | | ND | 26 |
| Error model | | Constant CV variance | Additive variance |
| Mean | | 23% | 0.13 |
| | | $E_{max}$ (μU/ml insulin) | $EC_{50}$ (GLP-1 pmol/l) |
| *Study 2* | | | |
| Mean ± SE by baseline glucose | <8 mmol | 34.5 ± 1.9 | 92.3 ± 32.2 |
| | >8–10 mmol | 48.6 ± 5.3 | |
| | >10–12 mmol | 69.1 ± 13.1 | |
| | >12 mmol | 136 ± 36 | |

MKC253 is glucagon-like peptide 1 (GLP -1, 7–36 amide) adsorbed onto technosphere microparticles for oral inhalation. The pharmacokinetics of inhaled GLP -1 and the pk-pd relationship between inhaled GLP -1 and insulin were analyzed in two trials, one in healthy normal volunteers and the other in patients with type 2 diabetes. Inhaled GLP-1 appeared to produce plasma levels of GLP-1 comparable to those of parenteral administration and sufficient to induce insulin secretion resulting in attenuation of postmeal glucose excursions in subjects with type 2 diabetes. An *Emax (maximum effect) model described the relationship between* GLP-1 concentration and insulin release.

Marino et al., Clinical pharmacology & Therapeutics | VOLUME 88 NUMBER 2 | August 2010



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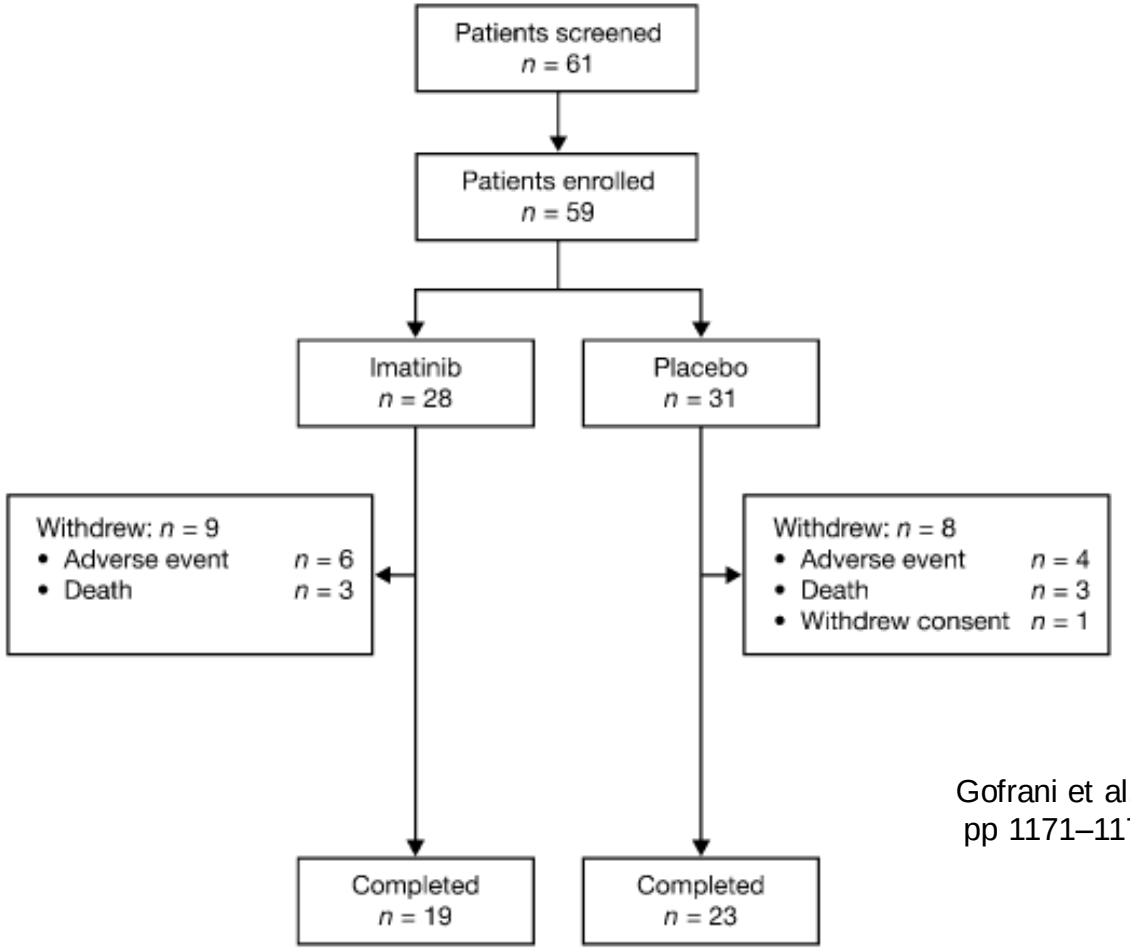
# Suitable patient populations –target population Pulmonary Arterial Hypertension-Example




Gofrani et al., Am J Respir Crit Care Med Vol 182. pp 1171–1177, 2010

*Figure 1.* Patient disposition in the intention-to-treat population.

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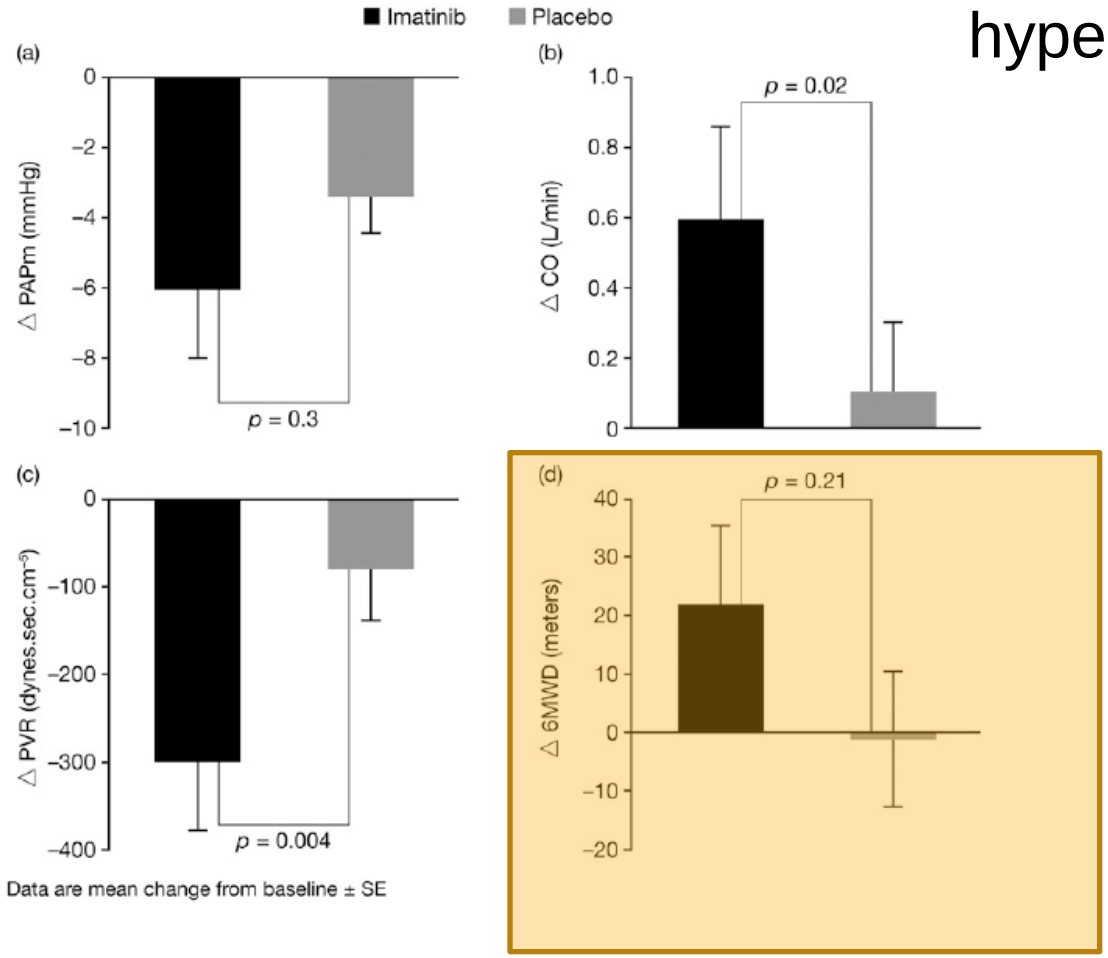
# Suitable patient population – target population

PoC trial in pulmonary arterial hypertension

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# Subpopulation identification - responders

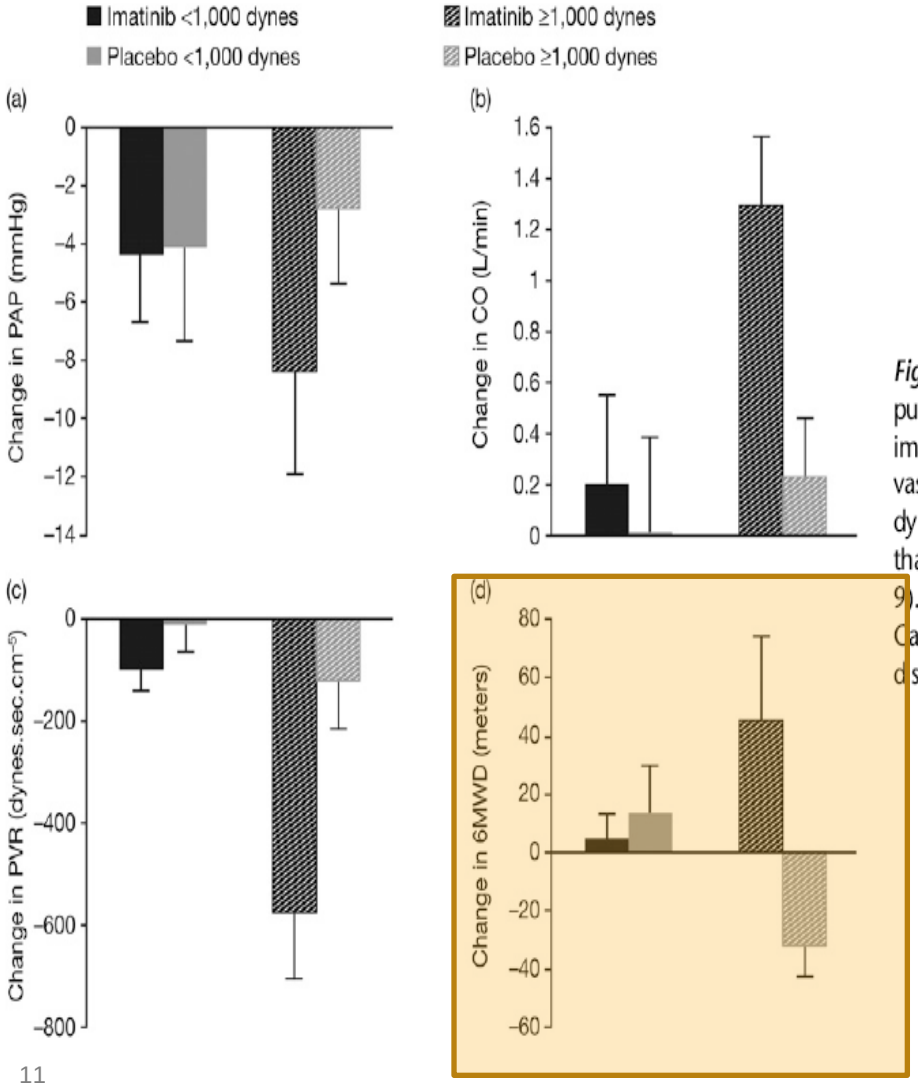


*Figure 3.* Mean change from baseline to study end in pulmonary hemodynamics in patients randomized to imatinib or placebo, stratified by baseline pulmonary vascular resistance (PVR) greater than or equal to 1,000 dynes · s · $cm^{-5}$ (imatinib n = 8; placebo n = 12) or less than 1,000 dynes · s · $cm^{-5}$ (imatinib n = 12; placebo n = 9). (*A*) Mean pulmonary artery pressure (PAPm). (*B*) Cardiac output (CO). (*C*) PVR. (*D*) 6-minute walking distance (6MWD).

Gofrani et al., Am J Respir Crit Care Med Vol 182. pp 1171–1177, 2010



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# Patient populations for rapid PoC

- Several approaches to pick the right PoC population are possible
  - Model diseases that are dependent from one factor
  - Primary disease
  - „Surrogate population“ due to similarity of disease biology
  - Healthy subjects if there is commonality with patient population
  - Target population with responder analysis
- All will have strengths and weaknesses
- Is PoC duration an important parameter for selection of the correct population?

# Part -2 Study designs for rapid PoC

- The simple answer:
  - Single dose
  - Fast read-out
  - Low sample size
  - Easy to recruit patient population
  - Parameters reading out quickly and with good signal to noise
  - Monocentric  and .....

  - The right site
  - Ethics Committee
  - Health Authority

# End of Presentation

..... If reality would not be different



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# Study designs

- Parameter selection
- Sampling density
- Treatment duration
- Statistics
- Trial tactics
- Operational setting

# Parameter selection - Surrogates with quick response – FEV1

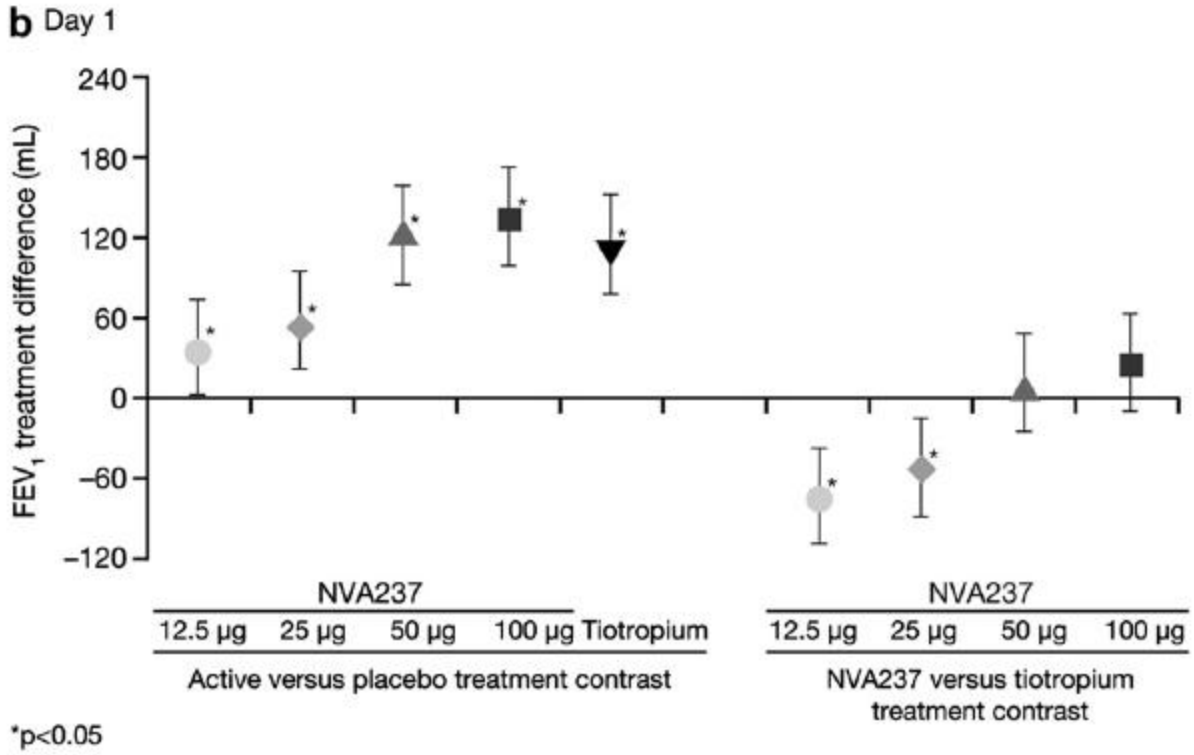


**Figure 2** Trough $FEV_1$ treatment contrasts (active versus placebo and NVA237 versus tiotropium; least square means, 95% confidence intervals) after (a) 7 days and (b) 1 day of treatment (mITT population). $FEV_1$ = forced expiratory volume in 1 s; mITT = modified intent-to-treat.

Verkindre et al Respiratory Medicine (2010) 104, 1482-1489



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# Parameter-selection: Fast functional read-outs relevant to disease

- **Cystic fibrosis with abnormal airway epithelial electrolyte transport leads to viscous airway secretions that are difficult to clear.**

- **By enhancing Cl- secretion onto and blocking Na+ absorption from the airway surface, treatment with aerosolized uridine 5'-triphophate (UTP) plus amiloride may improve the rheology of airway secretions and enhance mucociliary clearance**

- **Effects of inhaled vehicle and UTP/amiloride on mucociliary clearance of [99mTc] iron oxide particles from the airways of adult patients with CF (n = 14) are shown.**

Bennet et al. AM J RESPIR CRIT CARE MED 1996;153:1796 ff

# Mucociliary clearance effects in Cystic Fibrosis

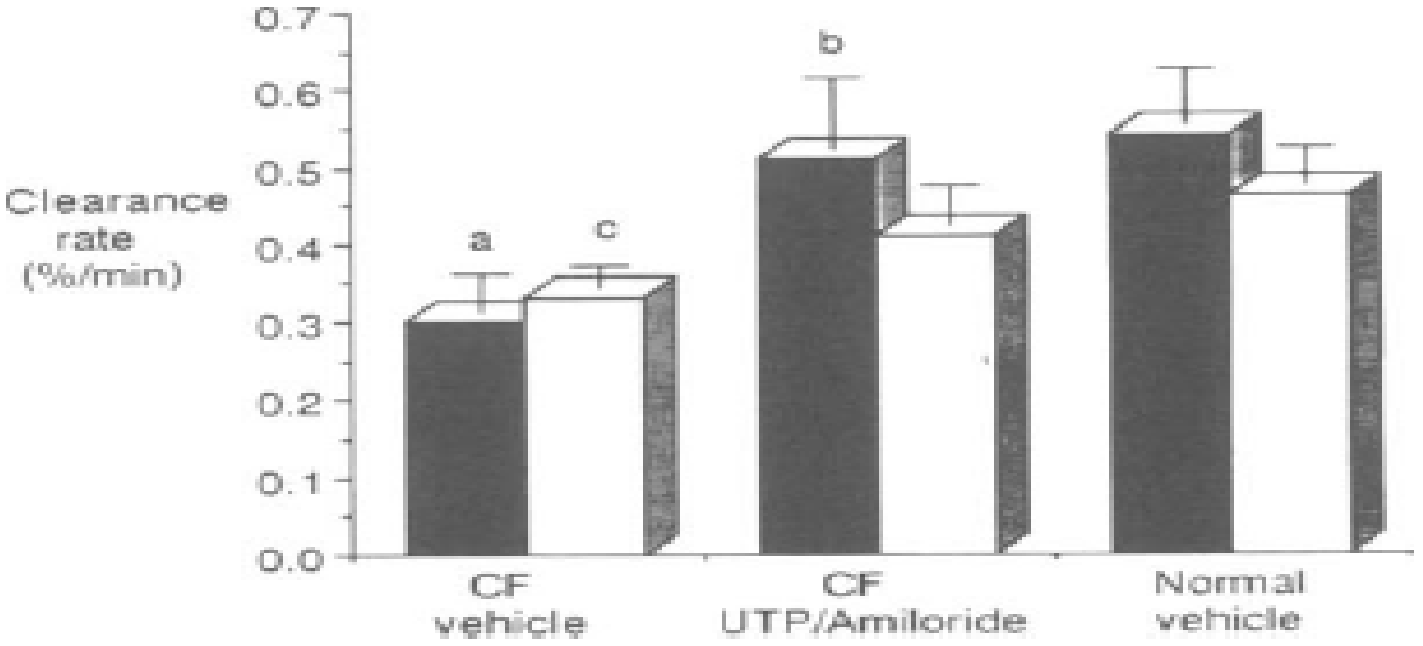


***Figure 4.*** The mean peripheral clearance rates through 40 (*closed columns*) and 80 (*open columns*) min in patients with CF (n = 14) for vehicle and UTP/amiloride compared with that in normal subjects (n = 12) for vehicle, (*a*) indicates significantly less than normal vehicle ($p = 0.01$); (*b*) indicates significantly greater than CF vehicle ($p = 0.04$), but not different from normal vehicle; (*c*) indicates significantly less than normal vehicle; ($p = 0.03$).



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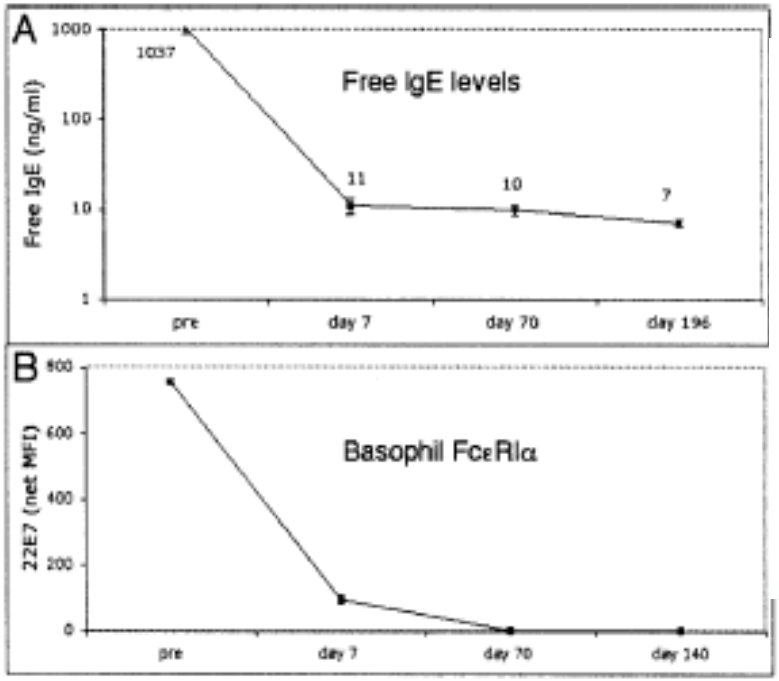
# Duration of the trial treatment

- What is the response dynamic of the biomarker or read-out
  - Functional response marker
  - Metabolic marker
  - Marker of Inflammation – Remodeling – Repair
- Pharmacokinetics
  - Elimination half-life; time to steady state of LMEs
  - Antibody (Tmax, Half life)

# FcεRI receptor downregulation in after Anti-IgE treatment-allerge challenge with house dust mite



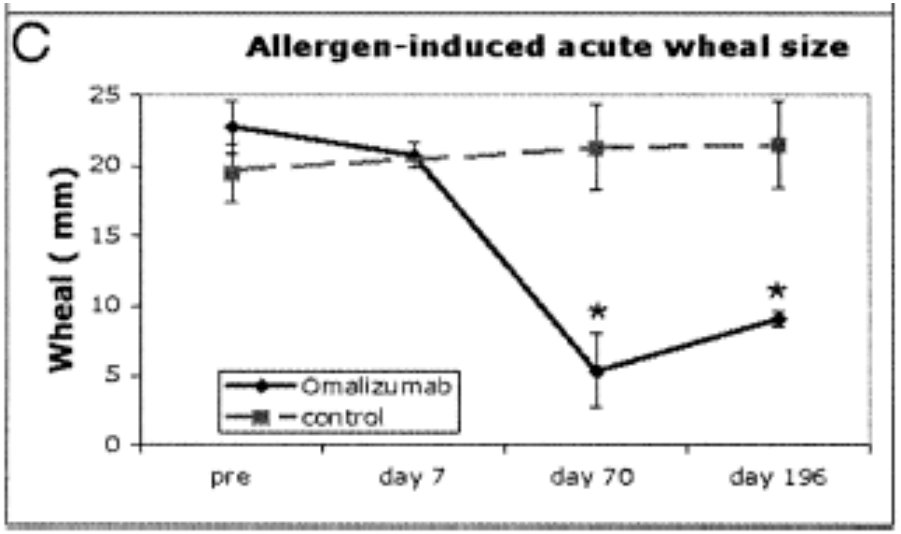




**FIG 1.** Free IgE levels influence basophil FcεRIα levels. **A**, Free IgE levels were reduced by greater than 99% by day 7 of omalizumab infusion and sustained through day 196. **B**, Basophil FcεRIα levels were reduced approximately 90% by day 7 and were undetectable after day 70 and day 140 of omalizumab treatment.

Beck et al. J Allergy Clin Immunol. 2004 Sep;114(3):527-30

➢Clinical response may not come at same time as biological response



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# Trial duration and design: cross-over vs. parallel group models

- Gain of cross-over models in terms of
  - Reduction in sample size (intraindividual vs. interindividual variability)
  - Less sites
  - Population recruitment rate
  - Less costs
- Loss of time by
  - Wash-out periods; sequence effects
- Issue of period effects

# Sampling scheme-repeated measurements

Table 2 Statistical analysis of the $FEV_1$ AUC values assessed as secondary efficacy variables (efficacy analysis set, ANCOVA model).

| Parameter | Day | Treatment | *n* | LS mean | SE | Contrast to placebo LS mean (95% CI)[a] | *P* value |
|---|---|---|---|---|---|---|---|
| $AUC_{0-5\ h}$ | 1 | Placebo | 33 | 1.849 | 0.0235 | | |
| | | NVA237 | 31 | 2.021 | 0.0242 | 0.172 (0.116, 0.228) | <0.001 |
| | 14 | Placebo | 32 | 1.744 | 0.0340 | | |
| | | NVA237 | 31 | 1.942 | 0.0346 | 0.198 (0.102, 0.294) | <0.001 |
| $AUC_{0-12\ h}$ | 7 | Placebo | 28 | 1.806 | 0.343 | | |
| | | NVA237 | 31 | 1.991 | 0.0325 | 0.185 (0.088, 0.282) | <0.001 |
| | 14 | Placebo | 32 | 1.714 | 0.0340 | | |
| | | NVA237 | 31 | 1.879 | 0.0346 | 0.165 (0.073, 0.257) | 0.001 |
| $AUC_{12-24\ h}$ | 14 | Placebo | 32 | 1.615 | 0.0339 | | |
| | | NVA237 | 31 | 1.776 | 0.0344 | 0.161 (0.079, 0.234) | <0.001 |

$FEV_1$ = forced expiratory volume in 1 s; AUC = area under curve; LS = least square; SE = standard error; CI = confidence interval.
[a] adjusted for baseline covariate.

Fogarty et al Respir Med. 2011 Mar;105(3):337-42

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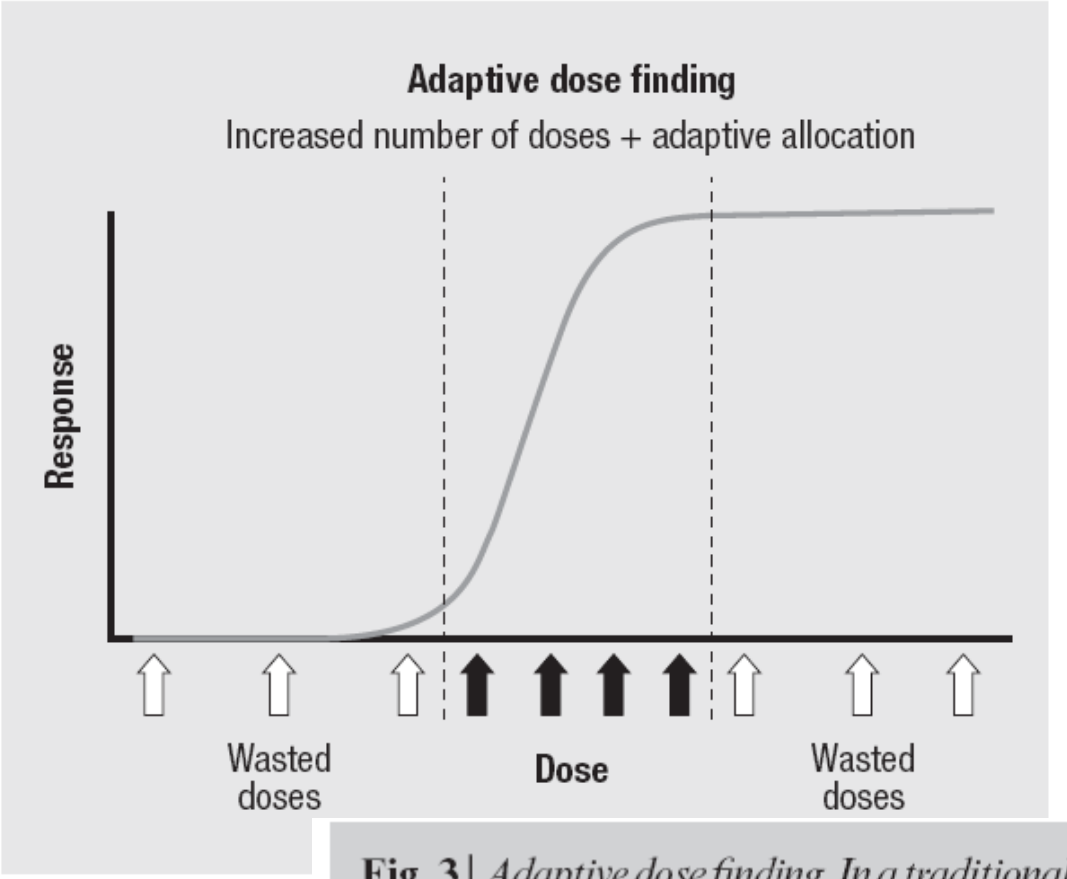
# Appropriate statistical approaches

- Bayesian approach
  - In a Bayesian analysis estimates of the treatment effect are obtained through the posterior distribution. According to Bayes' theorem the posterior is proportional to the likelihood of the **current** data multiplied with a **prior distribution**.
  - Assigning **study-specific weights** to the historical data sets included in the power prior, based on this degree of informativeness is possible.
  - In case of uncertainties very simple a priori assumptions can already help (such as the assumption of a monotone dose response)
  - Bayesian analysis for a given set of observations do not depend on **how many times the data** were analyzed previously or how many times in the future they may be analyzed.
  - Ongoing consideration of incoming data

# Adaptive designs




Orloff and Stanski; Ann Ist Super Sanità 2011 Vol. 47, No. 1: 8-13

**Fig. 3** | *Adaptive dose finding. In a traditional dose-finding trial, selecting a few doses may not adequately represent the dose-response relationship and many patients will be allocated to "non-informative" doses (wasted doses), as shown. In adaptive dose-finding, the strategy is to initially include only a few patients on many doses to explore the dose-response, then to allocate the dose range of interest to more patients. This reduces the allocation of patients to non-informative doses [29, 30].*



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# Interim read-outs

- Futility analysis
- Re-estimate of sample size (variability, effect size)
- Identification of responders, refinement of patient population
- DMC

# Operational setting

- Electronic data capture
- Telemedicine
- Ongoing medical review of incoming data

# Conclusion

Select the fastest setting but manage risk