

What is acceptable / ethical to test in healthy subjects?

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May 2019

What is acceptable in healthy subjects?

Content

- Set the scene: what happened before...
- Ethics in a historical context
- So what is acceptable?
- Summary & conclusion



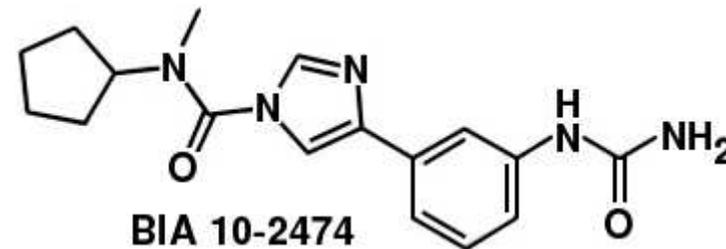
What is acceptable in healthy subjects?

Incidents happen: BIAL 10-2474

First-in-Human Clinical Trials — What We Can Learn from Tragic Failures

Sergio Bonini, M.D., and Guido Rasi, M.D.

On January 10, 2016, a healthy volunteer who had received 50 mg per day of a fatty acid amide hydrolase (FAAH) inhibitor for 5 days as part of a first-in-human phase 1 clinical trial was admitted to Rennes University Hospital with neurologic and gait disturbances. After a dramatic worsening of neurologic symptoms, the participant died on January 17.



N Engl J Med 2016; 375: 1717-1725

What is acceptable in healthy subjects?

Incidents happen & shape the future...

BAPU survey on SAEs: period 2009 - 2015

| | All | Young (<65 y) | | Elderly | |
|------------------|-----------------|-------------------|------------------|---------------|---------------|
| | | Male | Female | Male | Female |
| Total | 21,147 | | | | |
| Healthy subjects | 19,740 (93%) | 14,041 (71.1%) | 4,807 (24.4%) | 474 (2.5%) | 418 (2.1%) |
| Patients* | 1,407 (7%) | | | | |

*Special populations



What is acceptable in healthy subjects?

Incidents happen & shape the future...

BAPU survey on SAEs: period 2009 - 2015

| | Total #, incidence | | Related (#, %, incidence) | | | Unrelated (#, %, incidence) | | |
|---------------|-----------------------|----------|------------------------------|----|-----------|--------------------------------|-----|----------|
| SAE* SUSAR | 91 | 4.3 ‰ | 8 | 9% | 0.38 ‰ | 82 | 91% | 3.9 ‰ |

* At a total of 21,147 participants



What is acceptable in healthy subjects?

Incidents happen & shape the future...

Over the past 50 years:

- Worldwide: 12 deaths reported in phase 1 clinical trials
 - 5 possibly drug related
 - Underreporting...
- 50,000 to 100,000 subjects dosed / year
 - 2,5 to 5 million subjects over 50 years
- Risk of death is 1 in 500,000 subjects

(Alain Patat, BAPU meeting Dec 2016)



What is acceptable in healthy subjects?

Incidents happen & shape the future...

Over the past 50 years:

- Small number of drug related SAEs: <1 per 1000
- Small number of drug related fatalities: 1 per 500,000
- What is small? What is acceptable ...
 - Risk comparable to bungee jumping
 - Safer than: American football, scuba diving, sky diving, ...
 - ...



What is acceptable in healthy subjects?

Incidents happen & shape the future...

First-in-Human Clinical Trials — What We Can Learn from Tragic Failures

Clinical trials are still the best tool for providing the evidence needed for drug approval and appropriate clinical practice. Phase 1 trials are generally safe; there have been only two trials with very severe adverse events affecting several volunteers among the 14,700 studies (3100 first-in-human studies) involving 305,000 participants that have been conducted in the EU since 2005. It is hoped that the revised EMA guidelines, when available, will enhance strategies to identify and minimize risks for trial participants and to ensure that first-in-human trials throughout the EU member states are conducted in a safe, efficient, transparent, and harmonized manner for the benefit of human health.

N Engl J Med 2016; **375**: 1788-1789

What is acceptable in healthy subjects?

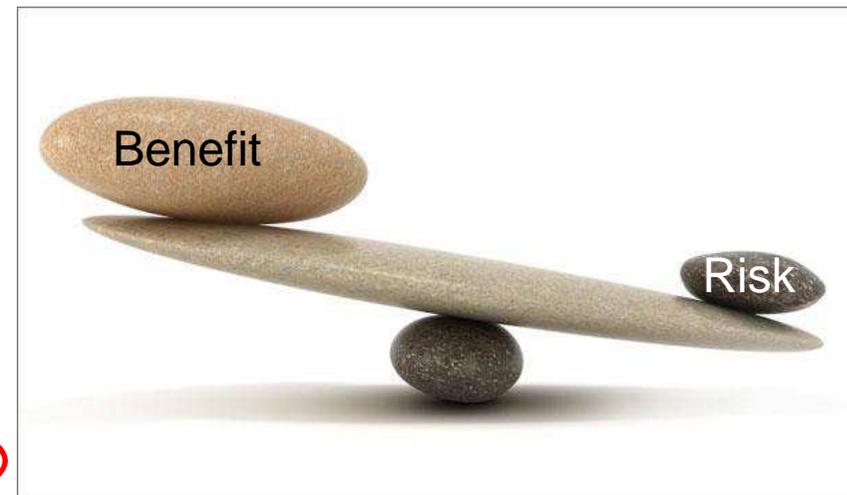
Incidents happen & shape the future...

TO THE EDITOR: Kerbrat et al. and Bonini and Rasi describe a phase 1 study that underwent review by an institutional review board. Nevertheless, I question whether it is ethical to enroll healthy persons in phase 1 (toxicity) trials.

According to the principle described in the Belmont Report,¹ beneficence implies a reasonable risk-to-benefit ratio. For a healthy volunteer enrolling in a toxicity trial, there is clearly risk but no medical benefit. Monetary compensation or appeals to altruism in the name of humankind are only avenues for ethical abuse. The only cohort that can be considered to derive at least a modicum of medical benefit from volunteering in a phase 1 trial consists of patients who have the condition for which the drug is being developed as a treatment. They should be the only persons who are asked to volunteer for a phase 1 trial.

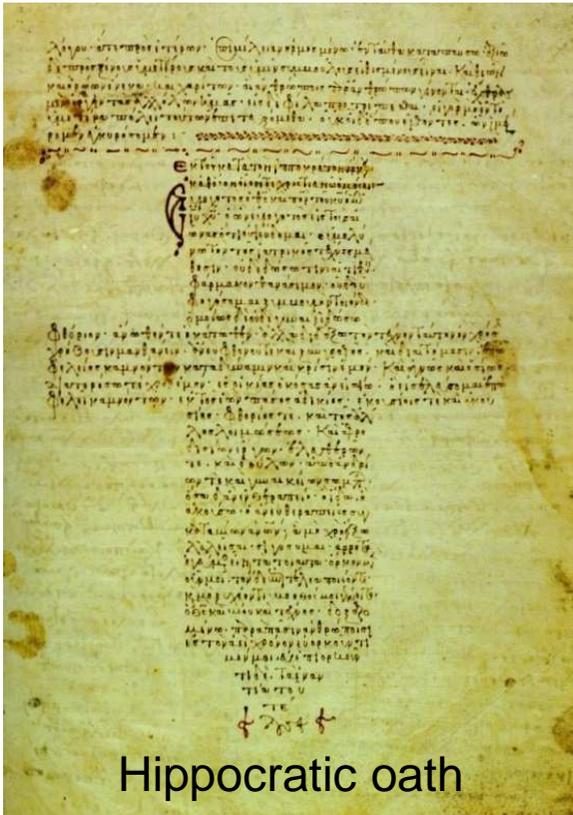
Irwin Nash, M.D.
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N Engl J Med 2017; **376**: 393

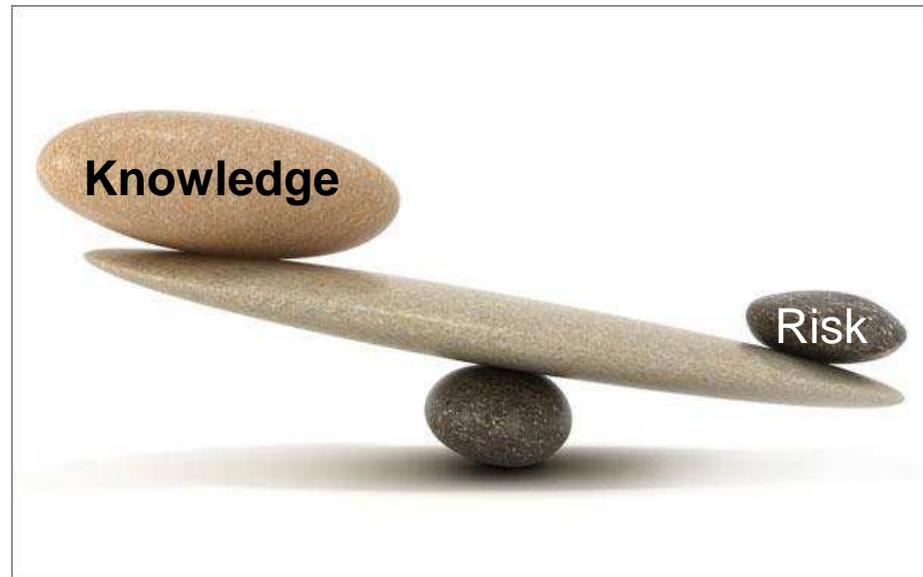


What is acceptable in healthy subjects? Primum non nocere...

Are phase I clinical trials in healthy subjects acceptable?



Societal benefit



What is acceptable in healthy subjects?

Primum non nocere...

OPINION

The risks of risk aversion in drug regulation

Nature Drug Rev Disc 2013; 12: 907-916



“... risk aversion comes with its own risks. Stakeholders should be aware that a drive towards an excessive focus on avoiding risks and uncertainties will mean that patients pay a price: delay in accessing therapeutics and lost therapeutic options.”

What is acceptable in healthy subjects?

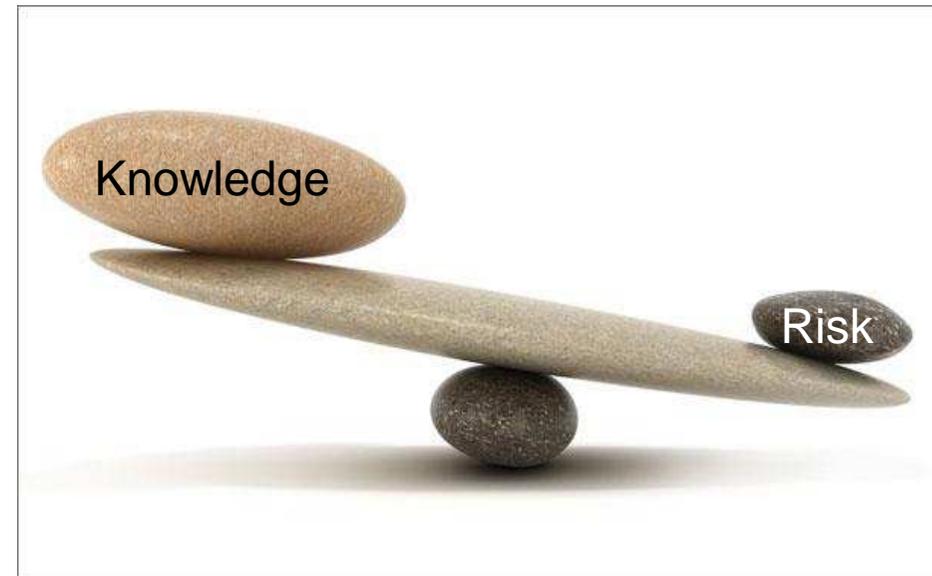
Primum non nocere...

Are phase I clinical trials in healthy subjects acceptable?

Declaration of Helsinki

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests...

Societal benefit



Incidents happen: lessons to learn? learning from past experiences...

1938 Food, Drug and Cosmetic Act

1947 Nuremberg Code

- post World War II trial of 23 doctors
- unethical experimentation
- Founder Dr. Leo Alexander, April 1947



Incidents happen: lessons to learn?

learning from past experiences...

- **Ten principles for human experimentation: Principle of **Voluntary Informed Consent****
 1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

Incidents happen: lessons to learn? learning from past experiences...

- **Ten principles for human experimentation (continued)**
 2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
 3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
 4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
 5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
 6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

Incidents happen: lessons to learn? learning from past experiences...

- **Ten principles for human experimentation (continued)**
 7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
 8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
 9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
 10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Basis for current regulations & ethical guidelines of clinical research

Incidents happen: lessons to learn? learning from past experiences...

- 1938 Food, Drug and Cosmetic Act
- 1947 Nuremberg Code
- 1961 Thalidomide disaster
- 1962 Kefhauer-Harris amendment (NDA)

1964 Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013



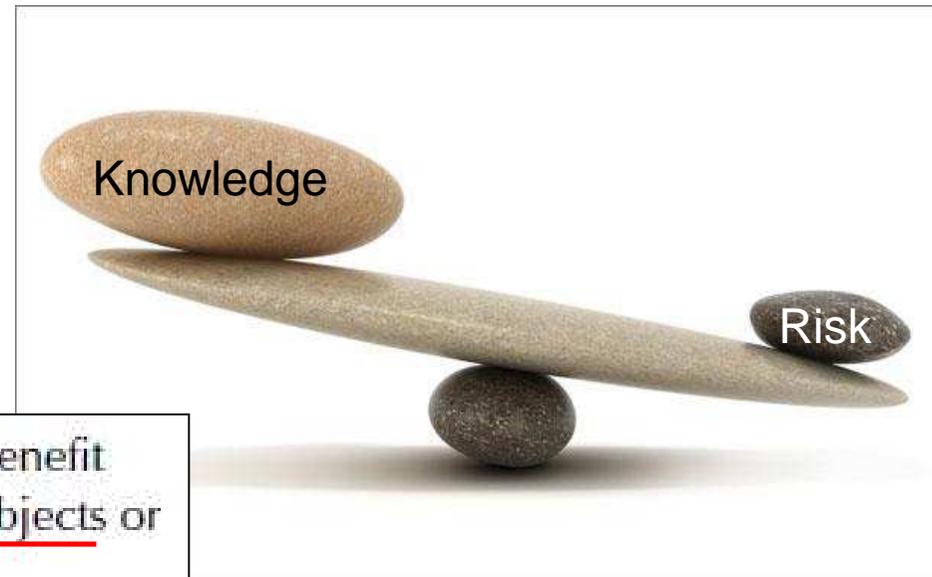
What is acceptable in healthy subjects?

Primum non nocere...

Are phase I clinical trials in healthy subjects acceptable? **YES**

Societal benefit

*Phase 1 research
(on healthy subjects)
is a “**necessary evil**”*



Clinical trials of an IMP that do not benefit subjects - whether they be healthy subjects or patients - are called phase 1 or non-therapeutic trials.⁷

What is acceptable in healthy subjects?

Primum non nocere...

Considerations:

- Likelyhood (of risk): low – high
 - mode of action?
 - nature of the target?
 - relevance of animal model?
- Duration: reversible – irreversible
- Intensity: mild – moderate – severe
- Benefit: health research – personal (payment) – commercial
- Population: healthy – patients – terminally ill
- Clinical equipoise: placebo – nocebo

What is acceptable in healthy subjects?

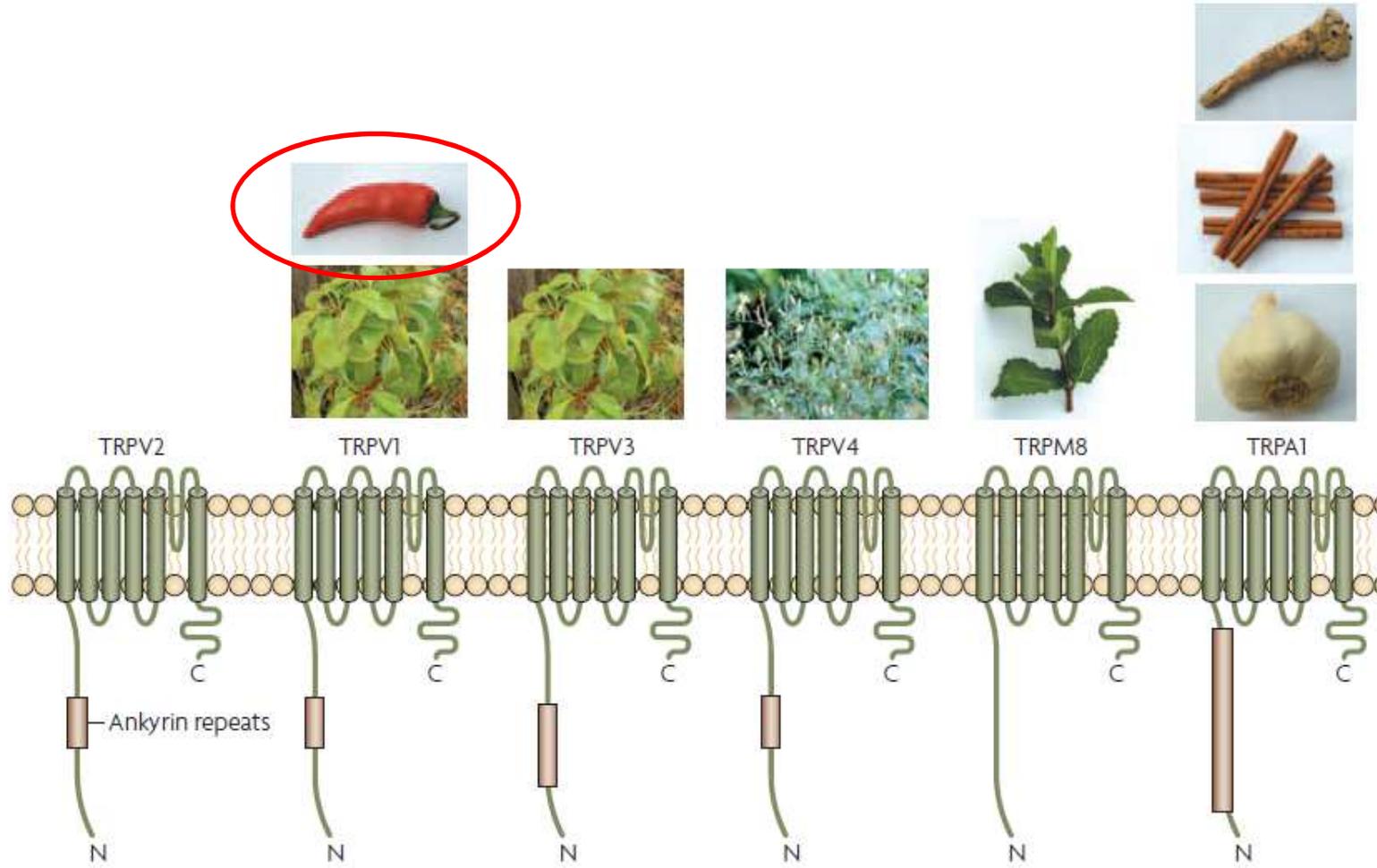
Challenge agents

| Challenge agent | Activity | Route of administration |
|-----------------|---------------------------|-------------------------|
| allergens | allergic reaction | skin prick / inhalation |
| acetylcholine | M-receptor agonist | inhalation / IA |
| histamine | H1- H2 agonist | skin prick / IA |
| isoprenaline | β -receptor agonist | IV |
| substance P | NK-receptor agonist | skin prick / IV / IA |
| serotonin | 5-HT agonist | IV / IA |
| P450 probes | CYP450 phenotypes | oral |

(Based on ABPI Guideline for phase 1 clinical trials, edition 2012)

What is acceptable in healthy subjects?

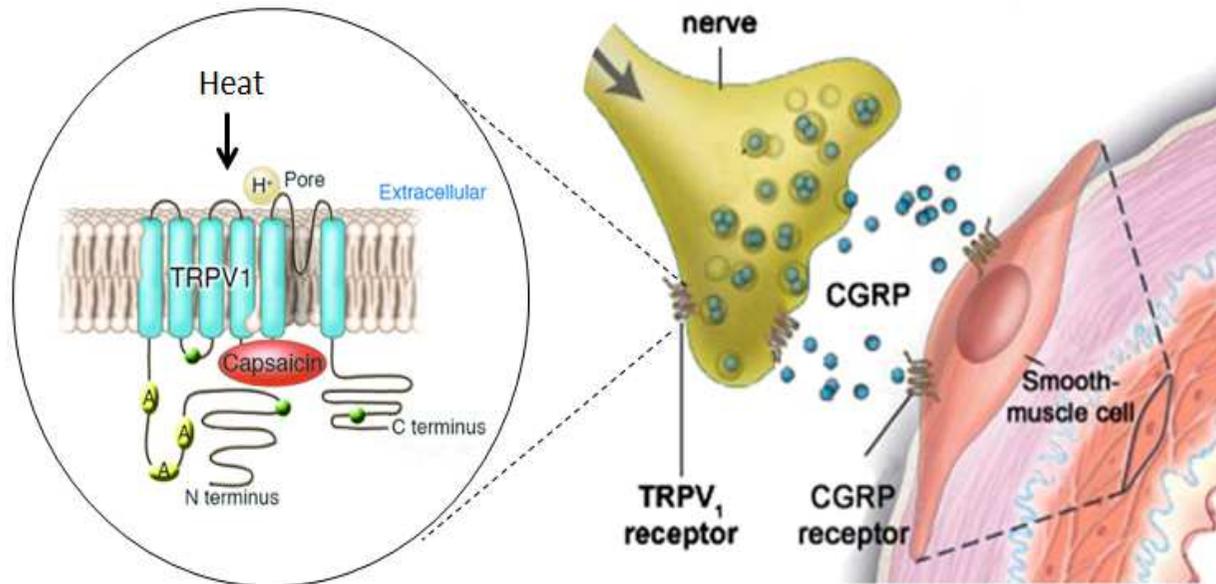
Challenge agents



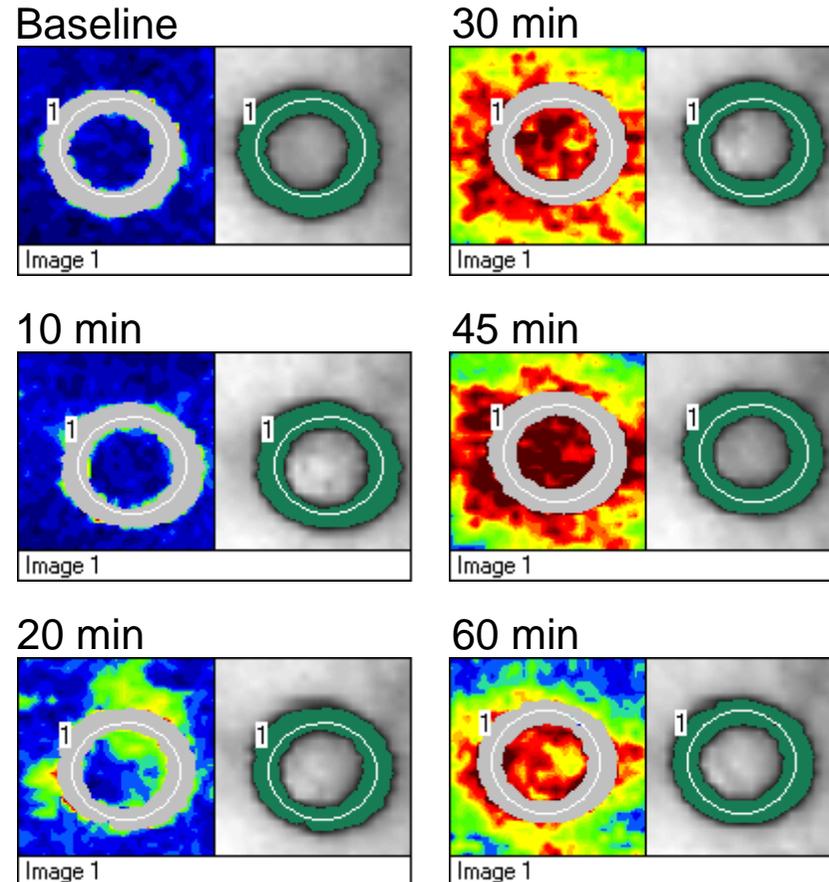
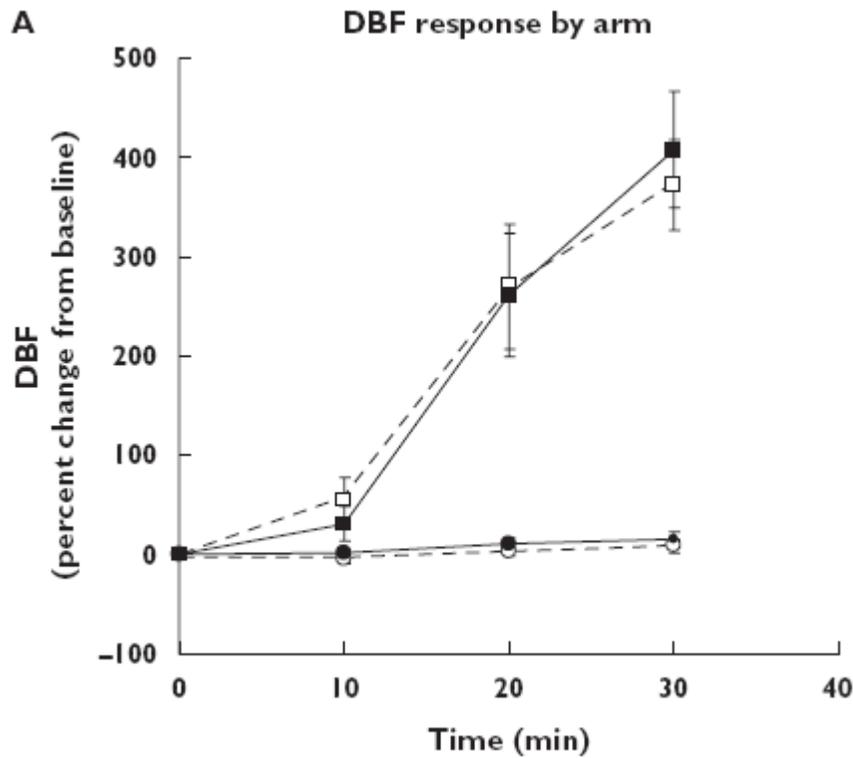
Nature Drug Rev Disc 2007; 6, 357-372

What is acceptable in healthy subjects?

Challenge agents

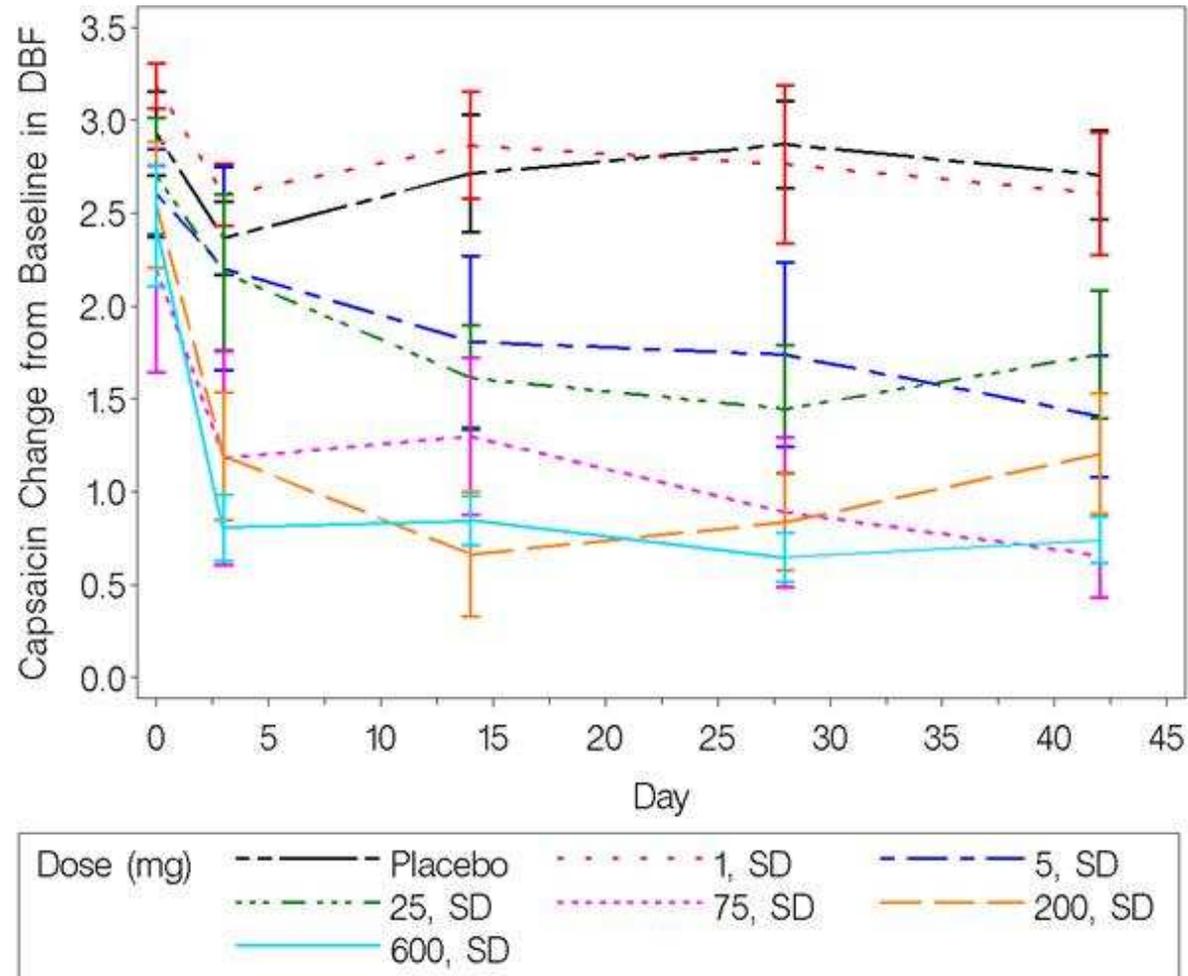


What is acceptable in healthy subjects? Challenge agents



Van der Schueren et al. *Br J Clin Pharmacol* 2007; 64: 580-590

What is acceptable in healthy subjects? Challenge agents with IMP



J. de Hoon et al., *Cephalalgia* 2013; vol 33(8 Suppl): 247-248, P367; (IHC Boston, 2013)

S. Vermeersch et al., *Cephalalgia* 2013; vol 33(8 Suppl): 249-250, P370; (IHC Boston, 2013)

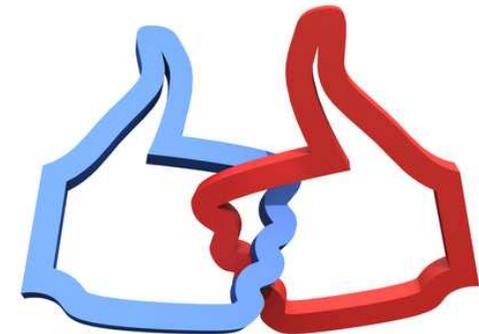


What is acceptable in healthy subjects?

Challenge agents with IMP

Phase I randomized, placebo-controlled study to determine the effect of mAb XYZ on biomarker response ABC in healthy male subjects

- Biological: mAb
- What about ADAs?
- After 6 months of follow-up, no return to baseline...



What is acceptable in healthy subjects?

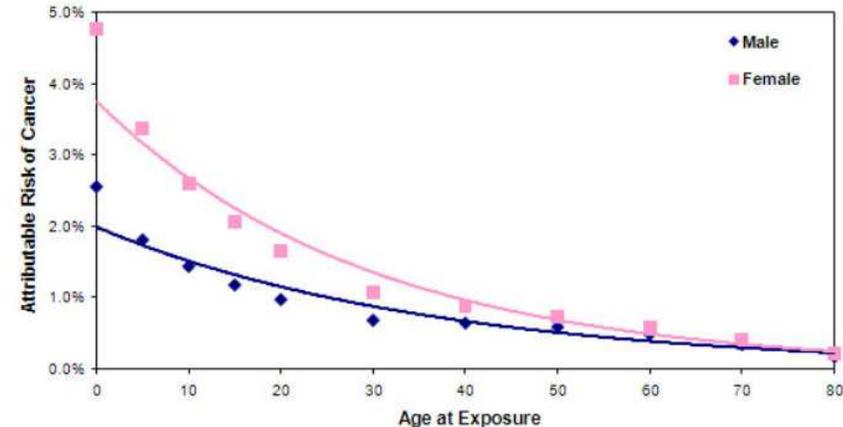
Radioactive challenge agent: microdosing

An open-label **PET** study of the occupancy of the ABC receptor by XYZ in healthy male participants

- Small molecule
- Risk of radiation exposure?
- CSF sampling better alternative?

Graph 1: Lifetime Attributable Risk of Cancer from Exposure to Radiation

Number of cases per 100,000 persons exposed to a single dose of 0.1 Gy



Adapted from the National Research Council. Health risks from exposure to low levels of ionizing radiation. BEIR VII Phase 2. Washington, DC: National Academies Press; 2006.

What is acceptable in healthy subjects?

Challenge agents inducing “disease-like” symptoms

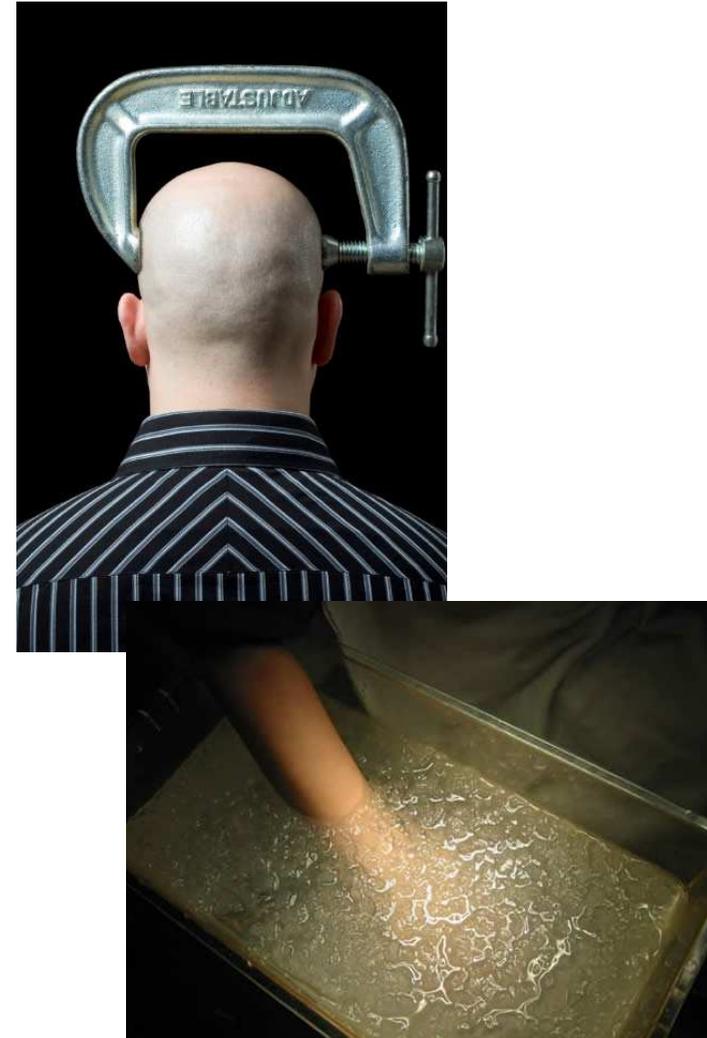
Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura

Jakob Møller Hansen, Anne Werner Hauge, Jes Olesen and Messoud Ashina
Cephalalgia 2010; 30: 1179-1186

Table 2. MA patients and controls reporting headache and migraine-like attacks after CGRP*

| Attack | MA patients | Controls | p value |
|--------------------------------------------------------|-------------|----------|---------|
| Migraine-like attacks (post-infusion phase 1–13 hours) | 8/14 | 0/11 | .003 |
| Headache (infusion phase 0–60 min) | 11/14 | 7/11 | .65 |
| Headache (post-infusion phase 1–13 hours) | 12/14 | 2/11 | .001 |

MA = migraine with aura; CGRP = calcitonin gene-related peptide.
 *Groups compared with Fisher’s exact test.

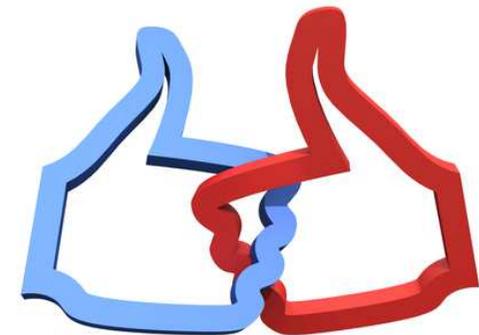


What is acceptable in healthy subjects?

Procedures...

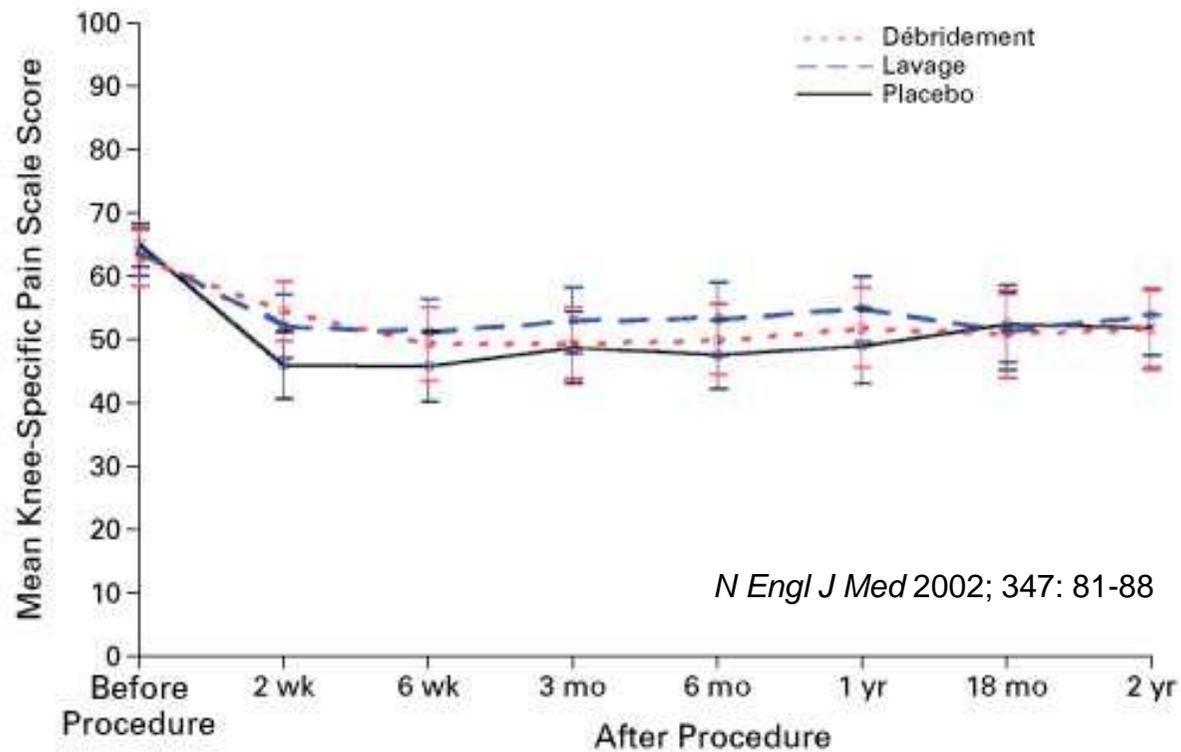
A multiple dose study to evaluate the safety, tolerability, and pharmacokinetics of XYZ in healthy male subjects

- Small molecule affecting gastric mucosa
- Requirement for gastroscopy with biopsy...
- What about other procedures?
 - CSF sampling
 - arterial cannulation
 - Quantative Sensory Testing (QST)
 - ...



What is acceptable in healthy subjects?

More procedures: sham interventions...



No. AT RISK

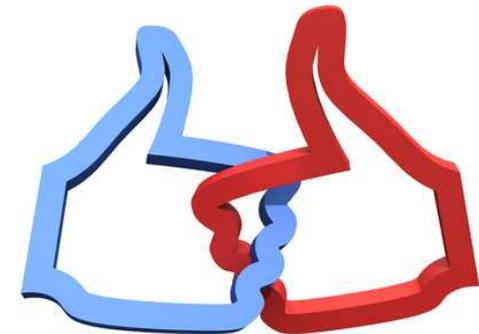
| | Before Procedure | 2 wk | 6 wk | 3 mo | 6 mo | 1 yr | 18 mo | 2 yr |
|-------------|------------------|------|------|------|------|------|-------|------|
| Placebo | 60 | 59 | 57 | 56 | 57 | 53 | 52 | 55 |
| Lavage | 61 | 59 | 57 | 59 | 59 | 57 | 56 | 55 |
| Débridement | 58 | 59 | 59 | 58 | 56 | 50 | 51 | 53 |

What is acceptable in healthy subjects?

“DART” testing in humans...

A randomized, double-blind, placebo-controlled phase 2 study to evaluate the effect of XYZ on **semen** parameters in adult males with ...

- Small molecule
- What about reversibility?



What is acceptable in healthy subjects? Inducing infections

HISTORY OF MEDICINE

The Challenges of Challenge Experiments

Susan E. Lederer, Ph.D.

N Engl J Med 2014; 371: 695-697

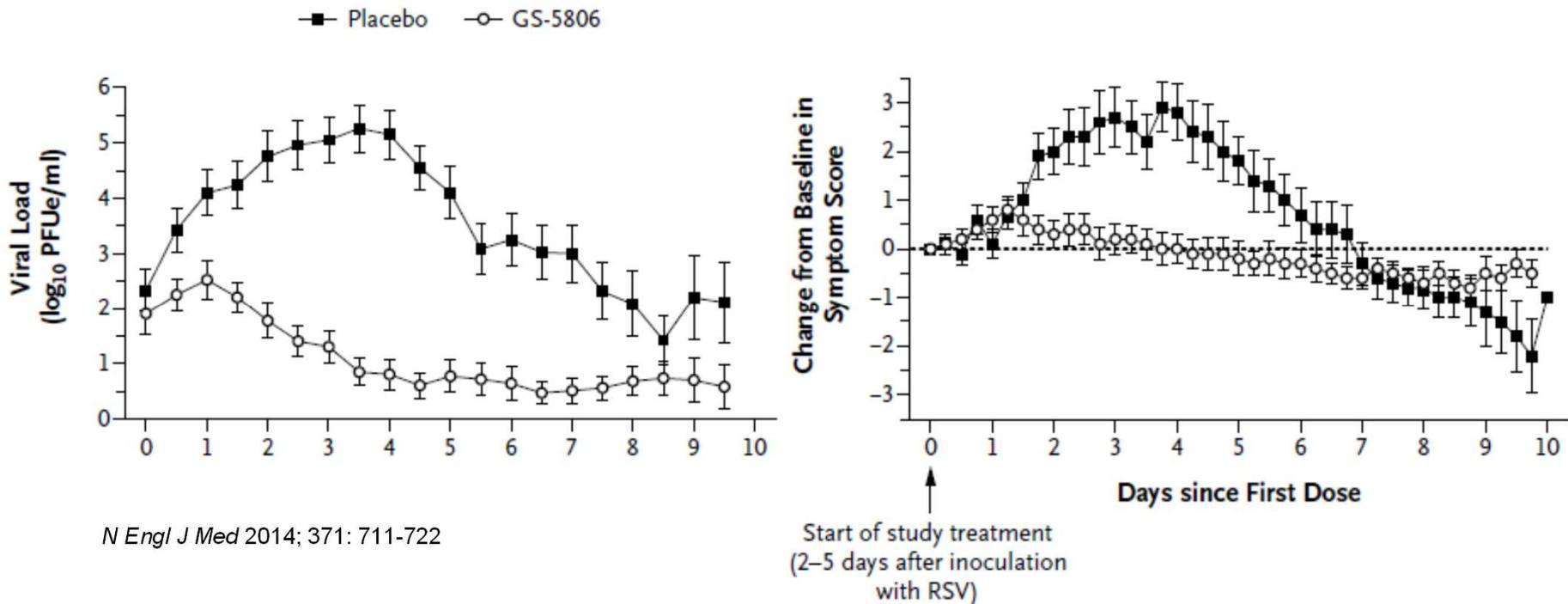


Lancet 2011; 11: 879-886

What is acceptable in healthy subjects? Inducing infections

ORIGINAL ARTICLE

Oral GS-5806 Activity in a Respiratory Syncytial Virus Challenge Study



N Engl J Med 2014; 371: 711-722

What is acceptable in healthy subjects?

Summary

*“Would you agree for
your child
to participate?”*



How acceptable are challenge agents? conclusion

- G
- E
- P

1493 - 1541



*"... all trials carry risks and there is no trial without a risk,
the only alternative to avoid any risk is not to participate."*



“If anything can go wrong, it will go wrong”

THE CHANGING LANDSCAPE OF EARLY
MEDICINES DEVELOPMENT: BE PREPARED!

