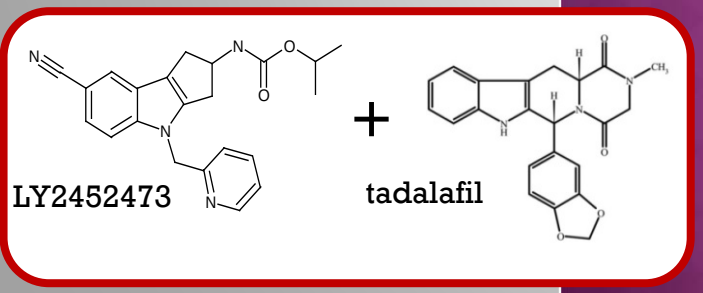
SARM I/TADALAFIL PHASE II COMBINATION STUDY FOR ERECTILE DYSFUNCTION

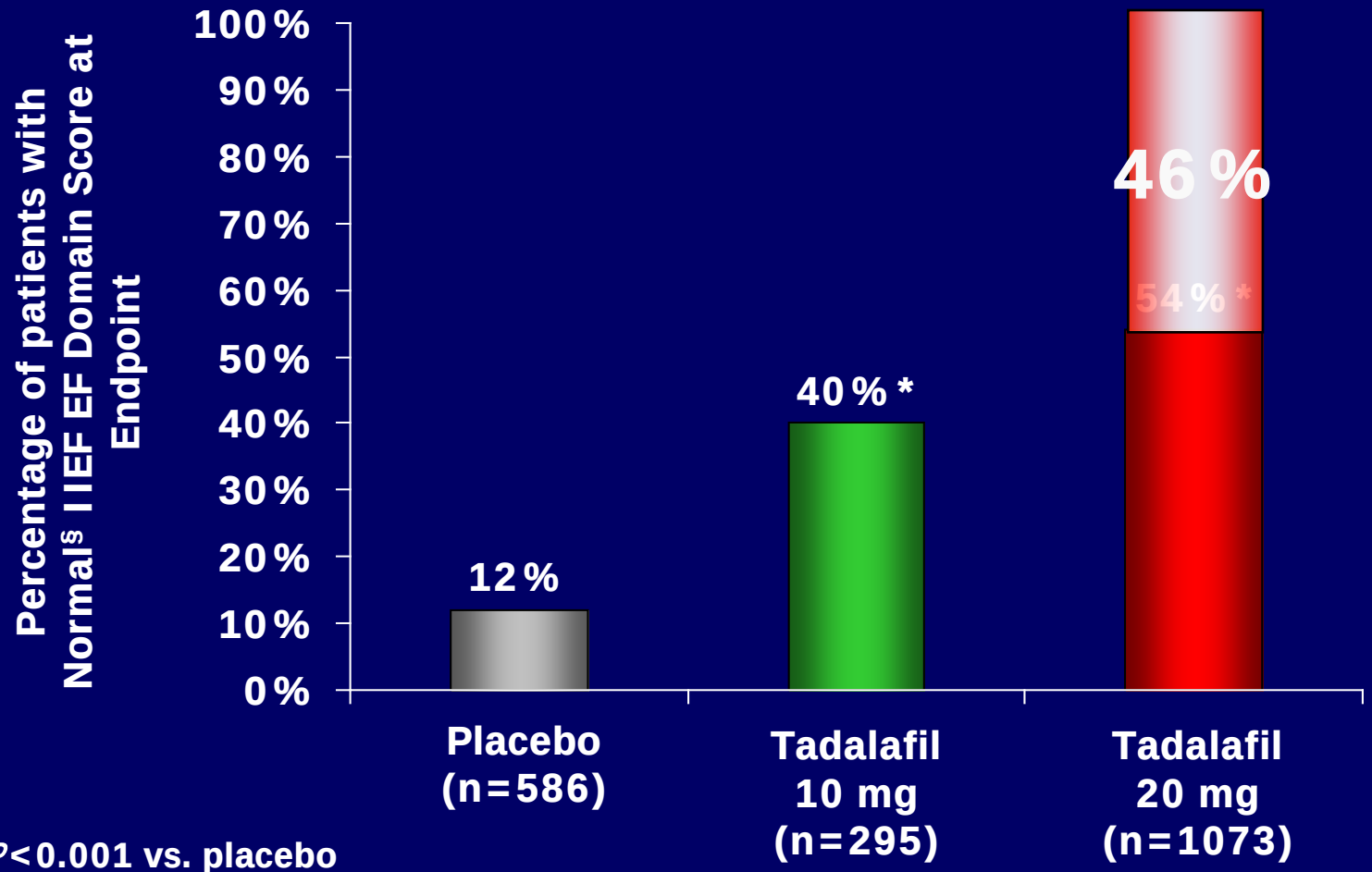
Modeling and Simulation to optimize study design

EMA EFPIA
Workshop on the importance of dose finding and dose selection
December 4, 2014



Charles Benson, MD, PhD
Senior Medical Director
Early Phase Medical
Eli Lilly and Company

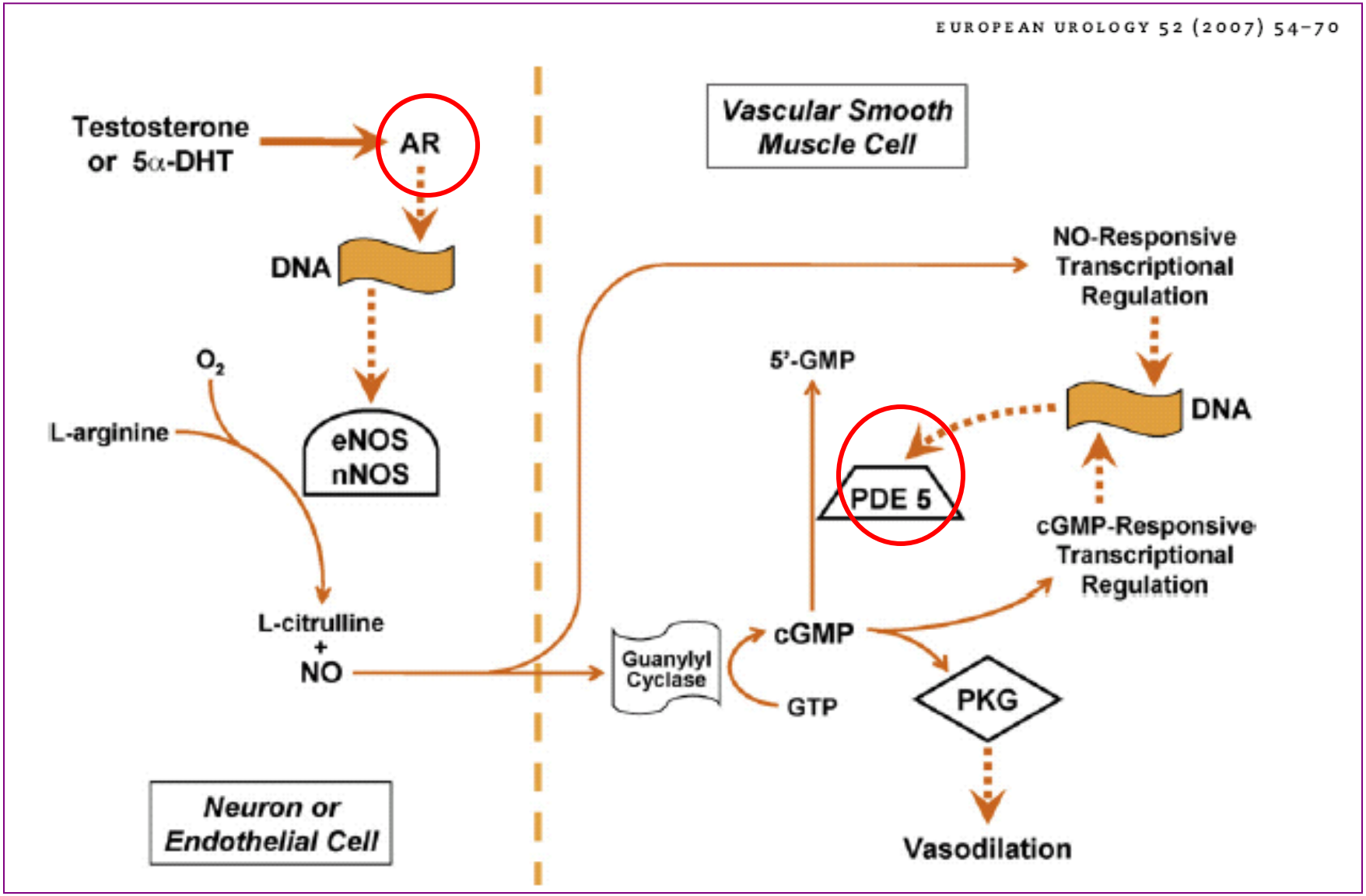
Efficacy: Percentage of Men Achieving Normal IIEF EF Domain Scores



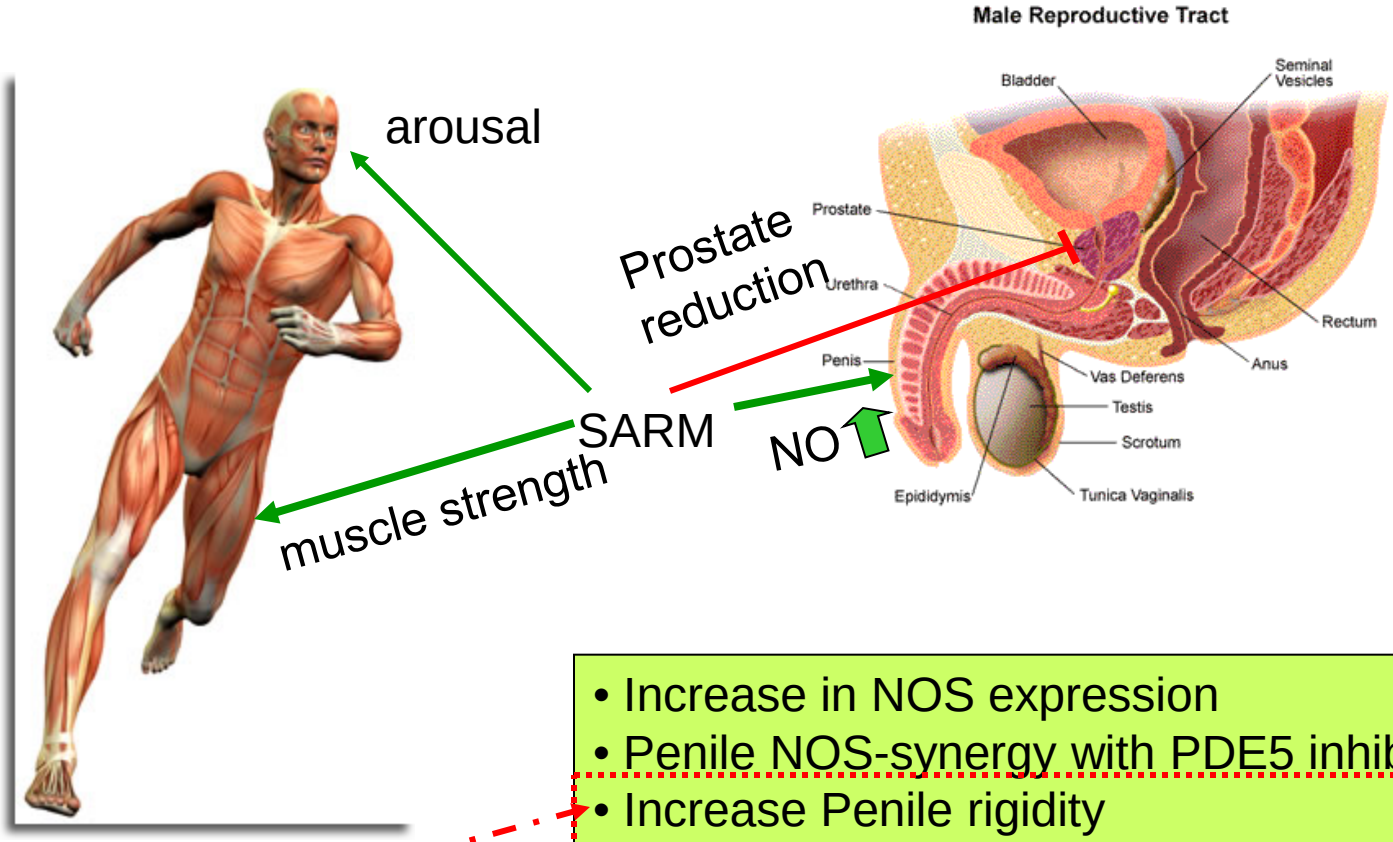
*P<0.001 vs. placebo
§ Normal defined as IIEF EF ≥26
n = number of patients with EF <26 at baseline and having a post-baseline EF domain score

Carson CC et al. BJU Int. 2004;93:1276-1281.

Mechanistic synergy when combining androgen and PDE5 inhibitors



Desirable attributes for a SARM to be combined with PDE5 inhibitor in ED



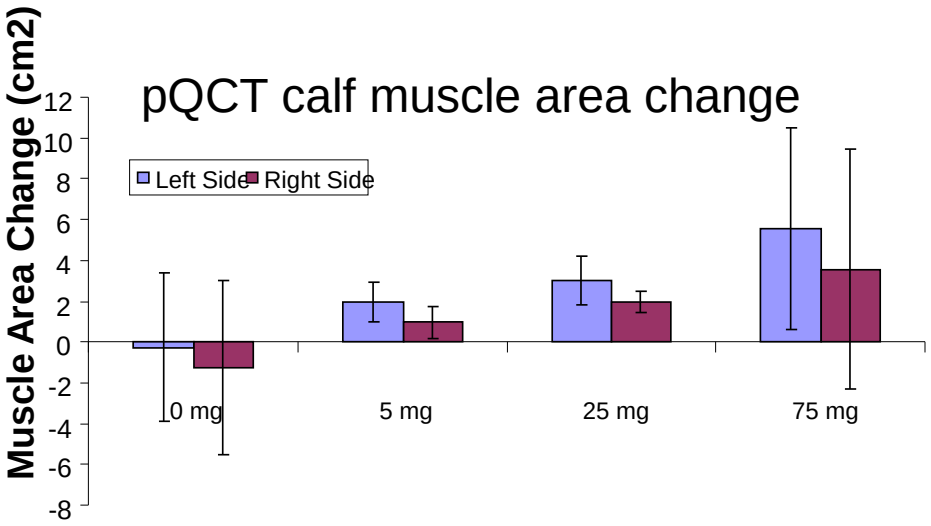
- Increase in NOS expression
- Penile NOS-synergy with PDE5 inhib
- Increase Penile rigidity
- Increase in ejaculatory function
- Increase in muscle strength
- Improved body composition less fat more muscle
- Differentiate on Prostate safety and CV risk
- Increase Sexual arousal

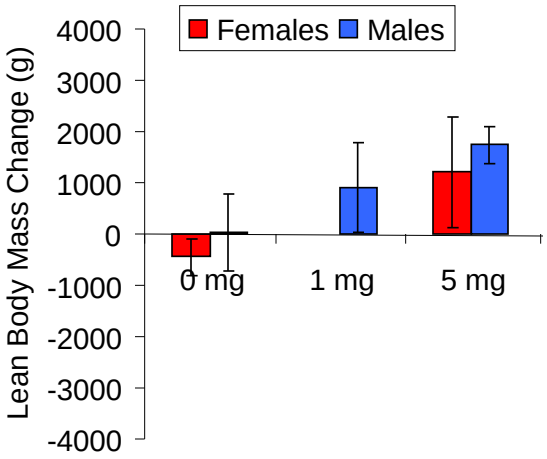
4

SELECTIVE ANDROGEN RECEPTOR MODULATOR (SARM)

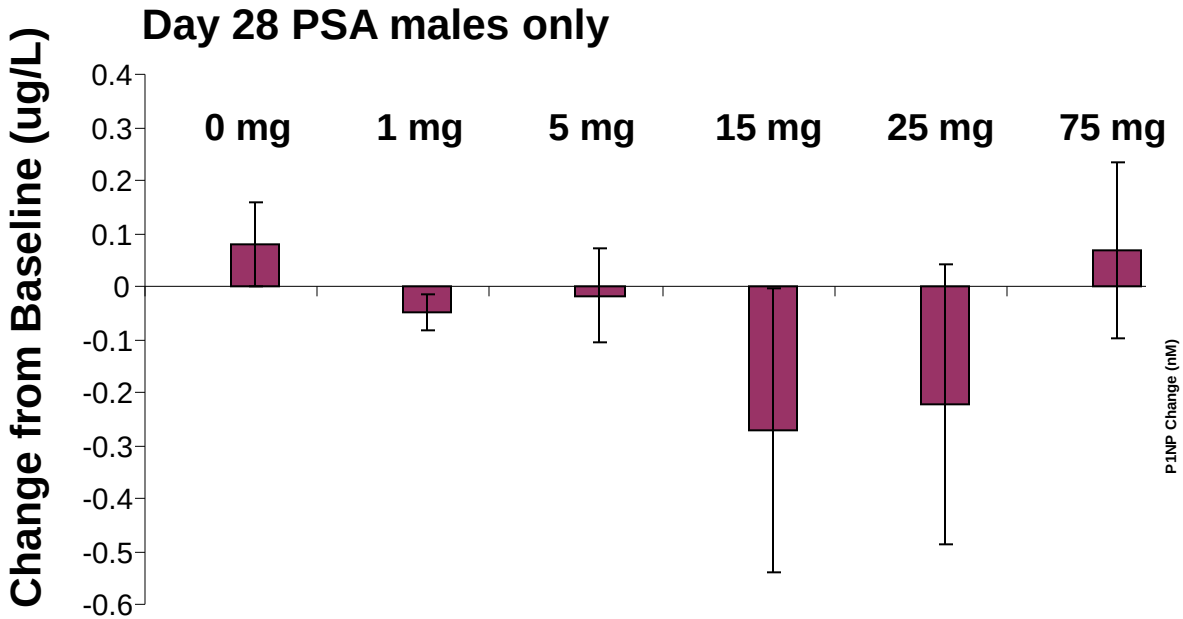
- Eli Lilly and Company has designed an oral, tissue-specific selective androgen receptor modulator (SARM) to provide agonist effects of an androgen on sexual function (nitric oxide synthase [NOS] and PDE5 expression, sexual arousal, and libido) with neutral or possible antagonistic effects on the prostate tissue

Phase I results from SARM I in healthy volunteers

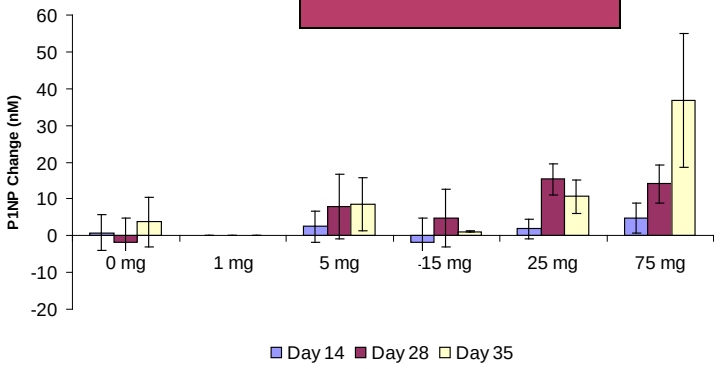




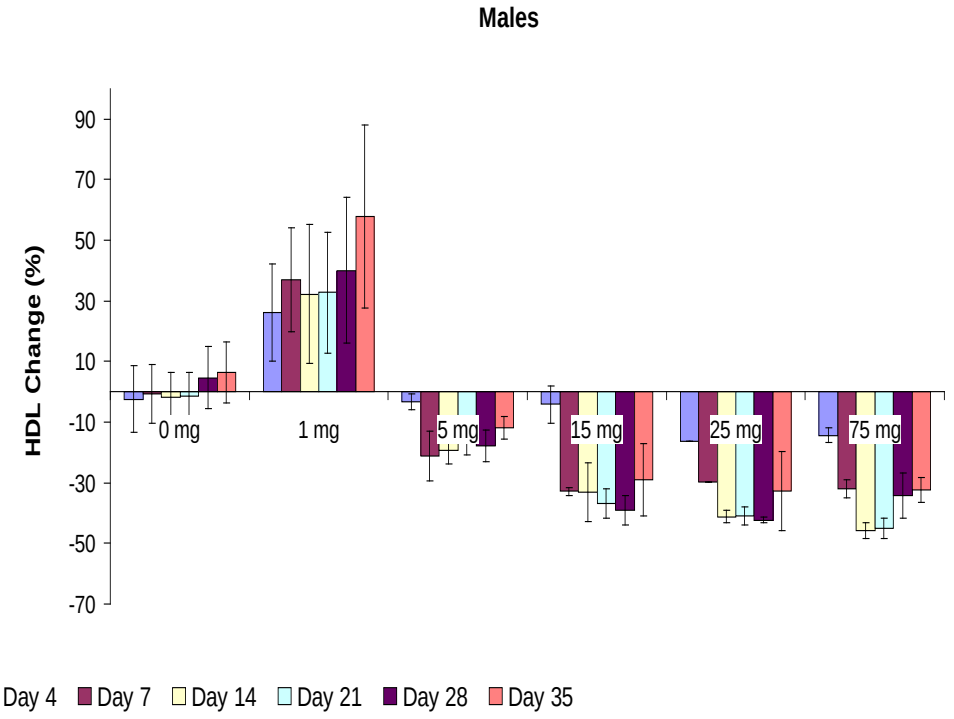
Lean muscle with DEXA

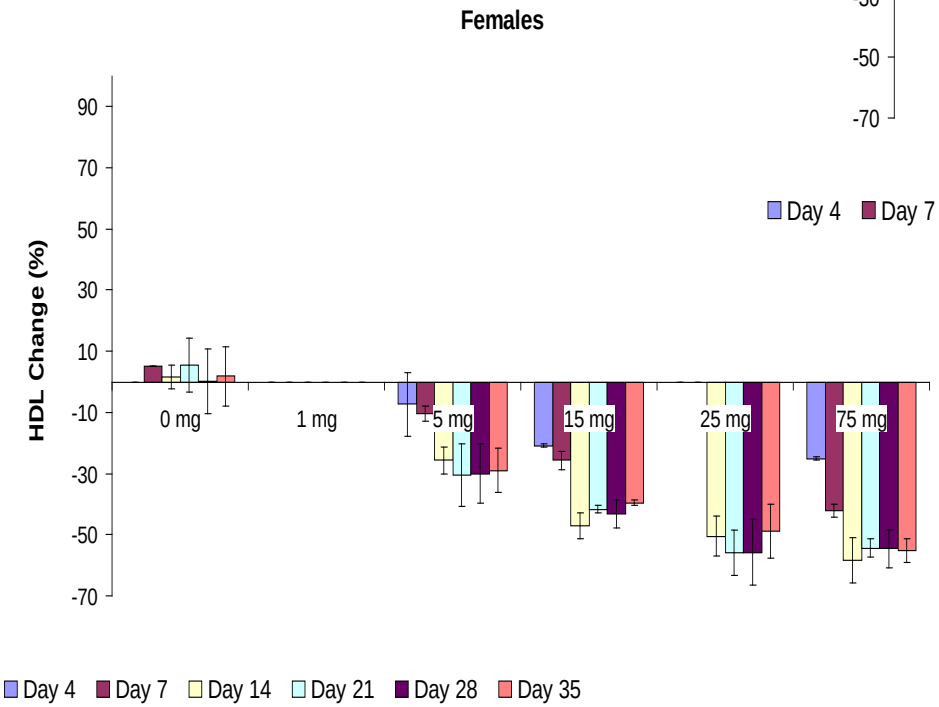


Serum P1NP



Phase 1 – 28 day HDL results





GUIDELINE ON CLINICAL DEVELOPMENT OF FIXED COMBINATION MEDICINAL PRODUCTS

For any individual fixed combination it is necessary to assess the potential advantages in the clinical situation against possible disadvantages…

a) an improvement of the benefit/risk due to:

i. addition or potentiation of therapeutic activities of their substances, which results in:

- a level of efficacy similar to the one achievable by each active substance used alone at higher doses than in combination, but associated with a better safety profile

or

- a level of efficacy above the one achievable by a single substance with an acceptable safety profile

ii. the counteracting by one substance of an adverse reaction (serious or commonly occurring) produced by another one.

b) a simplification of therapy by decreasing the number of individual dose units to be taken by the patient, which simplifies therapy and may improve patient compliance. This is also referred to as a "substitution indication".

European Medicines Agency

EFFICACY ARGUMENT - COMBINATION HAS TO BETTER THAN EITHER DRUG ALONE

- Historical Default Policy – The Factorial Study
  - A full factorial experiment is an experiment whose design consists of two or more factors, each with discrete possible values or "levels", and whose experimental units take on all possible combinations of these levels across all such factors
  - For example: If a design is denoted a 2^3 factorial, this identifies the number of factors (3); how many levels each factor has (2); and how many experimental conditions there are in the design ($2^3=8$).

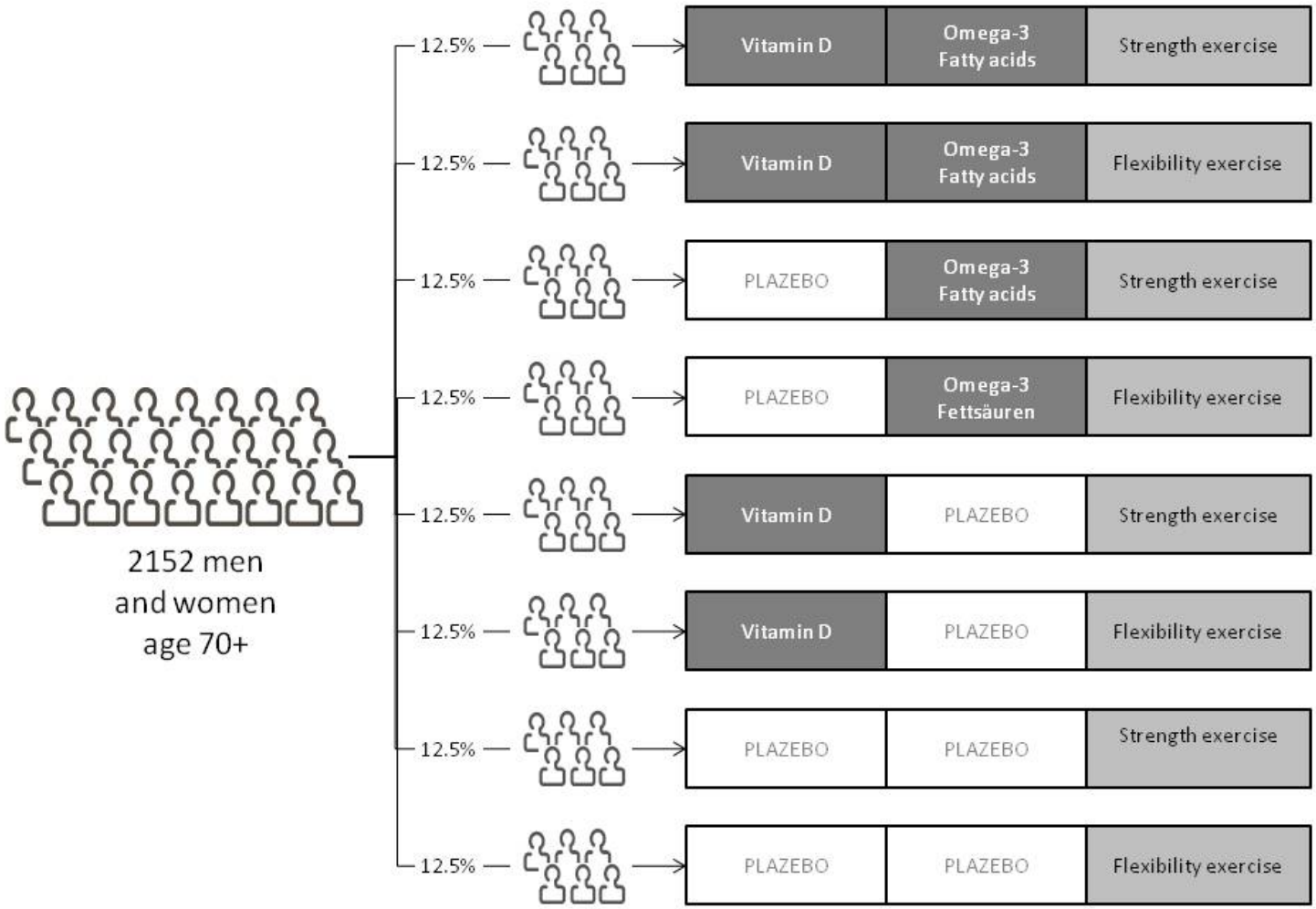
DO-HEALTH - VITAMIN D3 - OMEGA3 HOME EXERCISE- HEALTHY AGEING AND LONGEVITY TRIAL

- To establish whether vitamin D, omega-3 fatty acids, and a simple home exercise program will prevent disease at older age
- 2x2x2 factorial design trial
- 5 primary endpoints: the risk of incident non-vertebral fractures; the risk of functional decline; the risk of blood pressure increase; the risk of cognitive decline; and the rate of any infection.

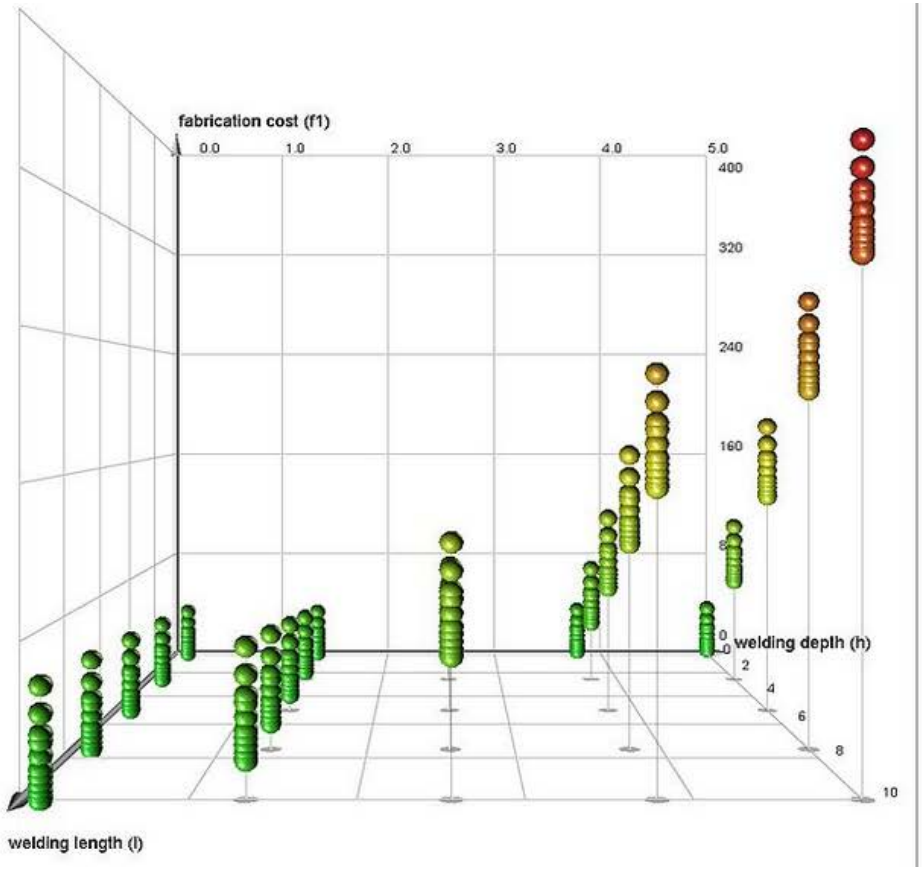
DO-HEALTH started in December 2012, and by November 22nd 2014, DO-HEALTH has recruited 2141 seniors age 70+. DO-HEALTH will be ongoing till 2017.

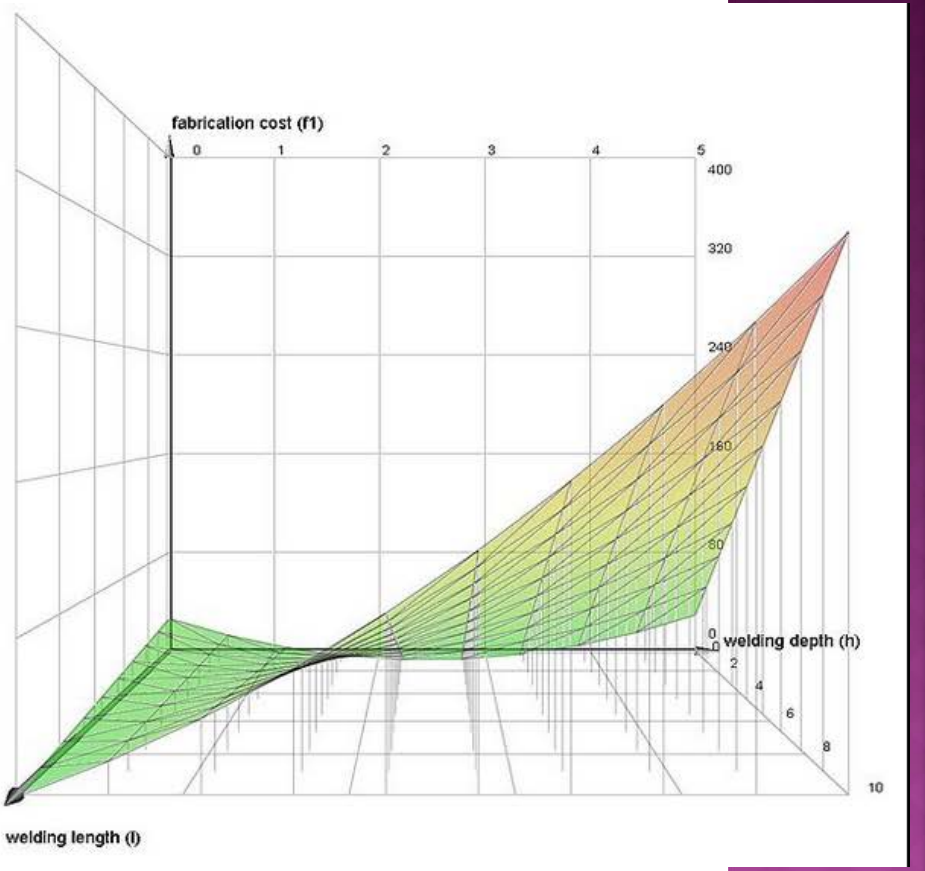
http://clinicaltrials.gov/ct2/show/NCT01745263

VITAMIN D3 - OMEGA3 HOME EXERCISE-HEALTHY AGEING AND LONGEVITY TRIAL



FACTORIAL DESIGN





Designed experiments with full factorial design (left), response surface (right). Number of factors (2); how many levels (5); $5^2 = 25$ experimental conditions

Factorial experiment. (2014, August 22). In *Wikipedia, The Free Encyclopedia*. Retrieved 19:09, November 22, 2014, from http://en.wikipedia.org/w/index.php?title=Factorial_experiment&oldid=622316407

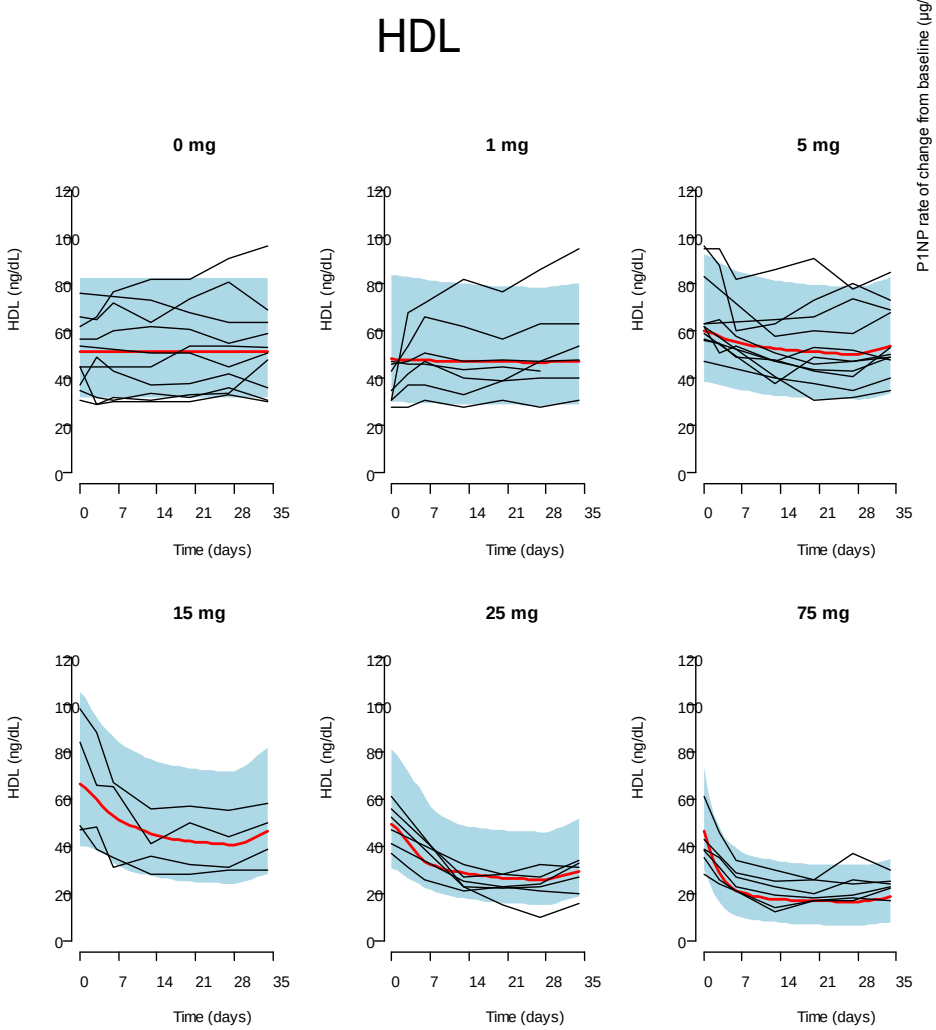
Efficacy Argument - Combination has to better than either drug alone

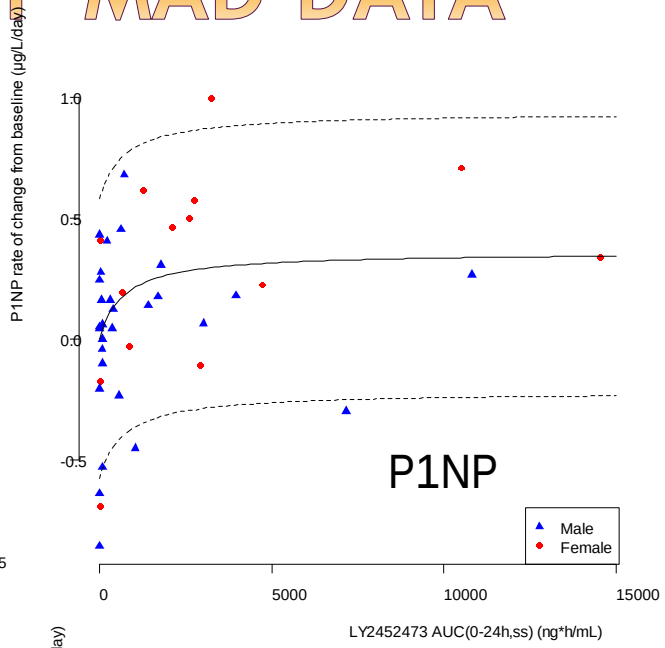
- The Factorial Study – fixed dose combination
  - Number of factors (2 - 3 drugs);
  - Levels each factor has (4 - 5 doses);
  - Number of arms (experimental conditions) there are in the design
    - 4 doses, 2 drugs; $4^2 = 16$ arms per study
    - 5 doses, 3 drugs; $5^3 = 125$ arms per study
- 16 to 125 arms makes full factorial design fixed dose combination studies impractical.
- Can modeling and simulation help with decreasing the number of arms?

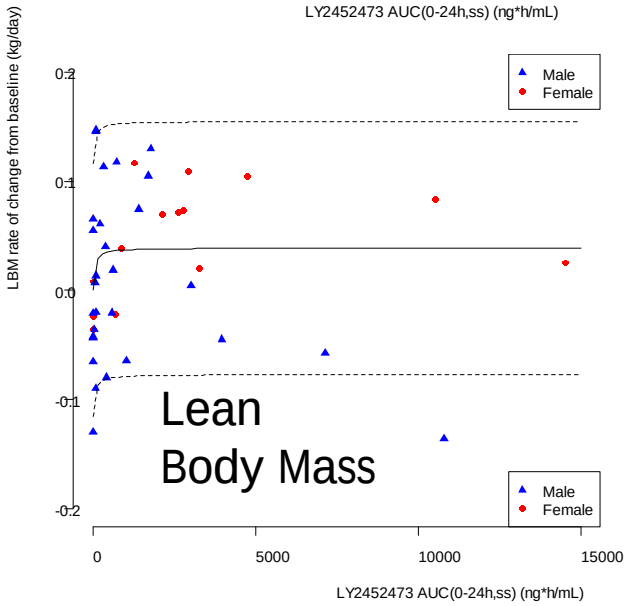
CAN WE LIMIT DOSES IN THE FIXED DOSE COMBINATION STUDY?

- Tadalafil alone dose arms of 5mg and 10mg per day
  - 5mg is currently marketed daily dose (must win against standard of care- active comparator)
  - 10mg – chosen to help define Emax in this population (combination must beat simply raising the dose of existing PDE5i)
- SARM Doses?
  - Simulations were conducted to determine the maximum Phase 2 dose which is likely to result in an acceptable HDL risk while still achieving adequate bone and muscle efficacy.

PK/PD MODELLING OF MAD DATA

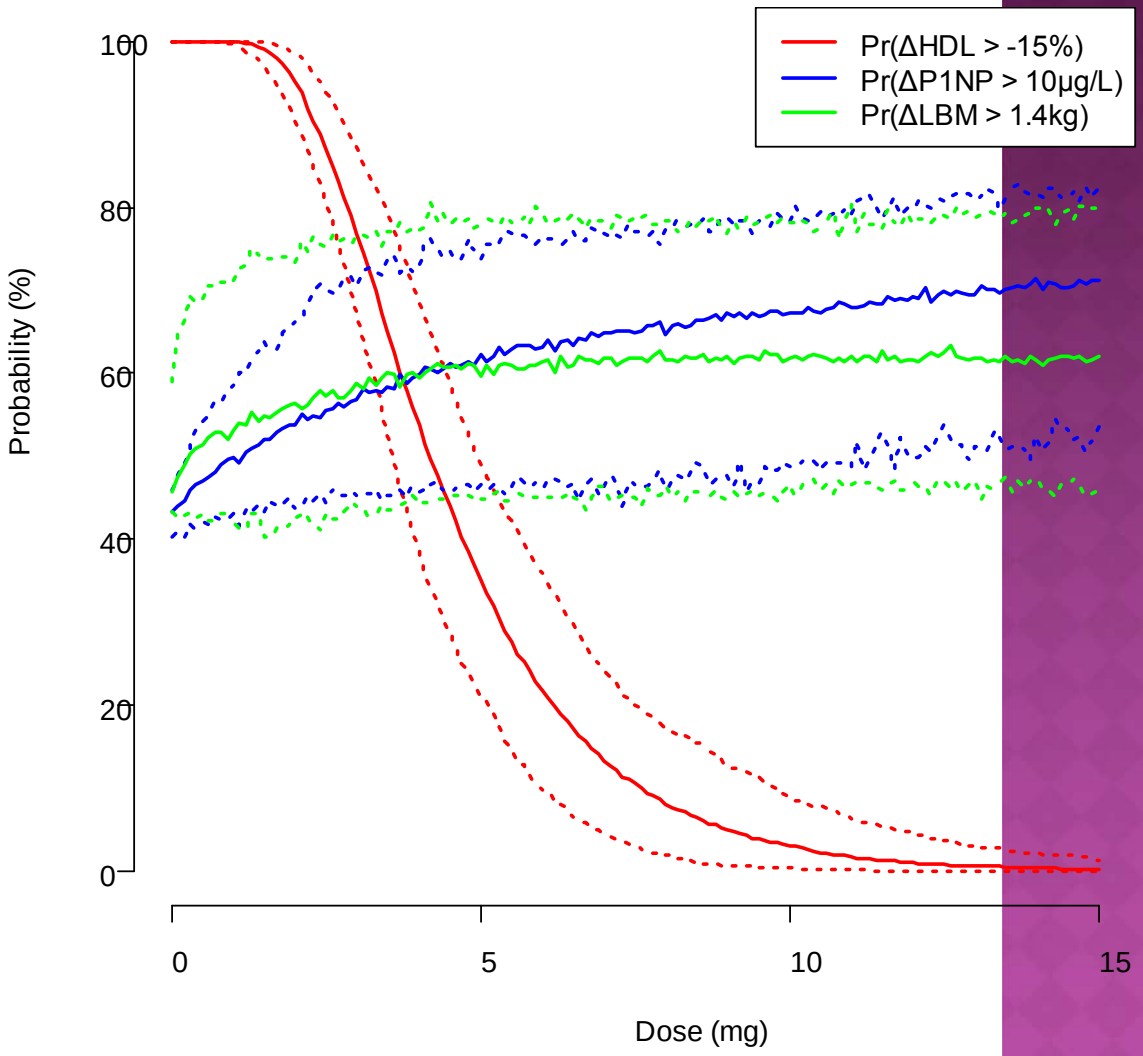






PK/PD MODELLING: PROBABILITIES OF ACHIEVING SAFETY AND EFFICACY AT 6 MONTHS

- 151 dose levels: 0 to 15 mg in steps of 0.1 mg
- For each dose level, simulate 10,000 patients
- 1,510,000 simulated patients in total
- Each patient is assigned a random AUC based on PK variability, and this AUC is fed into the PD model to produce the predicted response (including variability from the PD model).
- At each dose level we have 10,000 simulated observations, which results in a distribution of predicted responses.
- Probabilities of achieving stated cutoff values (plotted here) are calculated from these distributions for each dose level.
- Entire process is repeated 100 times, accounting for model uncertainty by resampling from original dataset and refitting models – this gives the 90% prediction intervals shown as dashed lines on the plot.



SARM 1 PHASE 2 DOSE SIMULATIONS

1. Lean body mass, P1NP and HDL responses are simulated from either 120 or 160 subjects, based on their simulated PK
   - Placebo arm plus either 2 or 3 LY arms, with 40 subjects/arm
2. Separate exposure-response models are fitted for each response, and the parameters are stored (EE50 and E_{max})
3. The process is repeated 1,000 times, and the CV% for each parameter is estimated based on the variability of the fitted parameter values
4. Steps 1-3 are repeated 100 times to assess the variability in the estimated CV%

LEAN BODY MASS

Doses (mg)	CV(EE50) (%)	CV(E_{max}) (%)	Failure rate (%)
1, 3, 5	19.8 (13-144)	103 (57.1-607)	1.65 (0.3-5.21)
1, 5	18.5 (12.7-36.8)	111 (56.4-757)	1.5 (0.4-4)
2, 5	17.3 (11.4-25.1)	108 (60.5-459)	3.1 (1.49-7.1)
2, 4	17.1 (10.5-30.5)	102 (62.7-236)	3.1 (1.19-8.75)
3, 5	16.7 (11-35)	100 (64-181)	3.8 (1.89-10.7)

Expected precision and failure rates (and 90% prediction intervals thereof, based on model uncertainty, in parentheses) of exposure-response models for lean body mass in potential Phase 2 studies

P1NP

Doses (mg)	CV(EE50) (%)	CV(E_{max}) (%)	Failure rate (%)
1, 3, 5	15.1 (11.8-29)	60.8 (46.5-127)	0 (0-0.405)
1, 5	14.3 (10.8-23.5)	64.5 (49.7-123)	0.1 (0-0.415)
2, 5	13.6 (10.7-31.5)	61.6 (47.6-138)	0 (0-0.205)
2, 4	12.4 (9.33-20.8)	59.2 (44.5-84)	0 (0-0.2)
3, 5	13.7 (10.2-76.1)	62.1 (47-281)	0 (0-0.215)

Expected precision and failure rates (and 90% prediction intervals thereof, based on model uncertainty, in parentheses) of exposure-response models for P1NP in potential Phase 2 studies

HDL

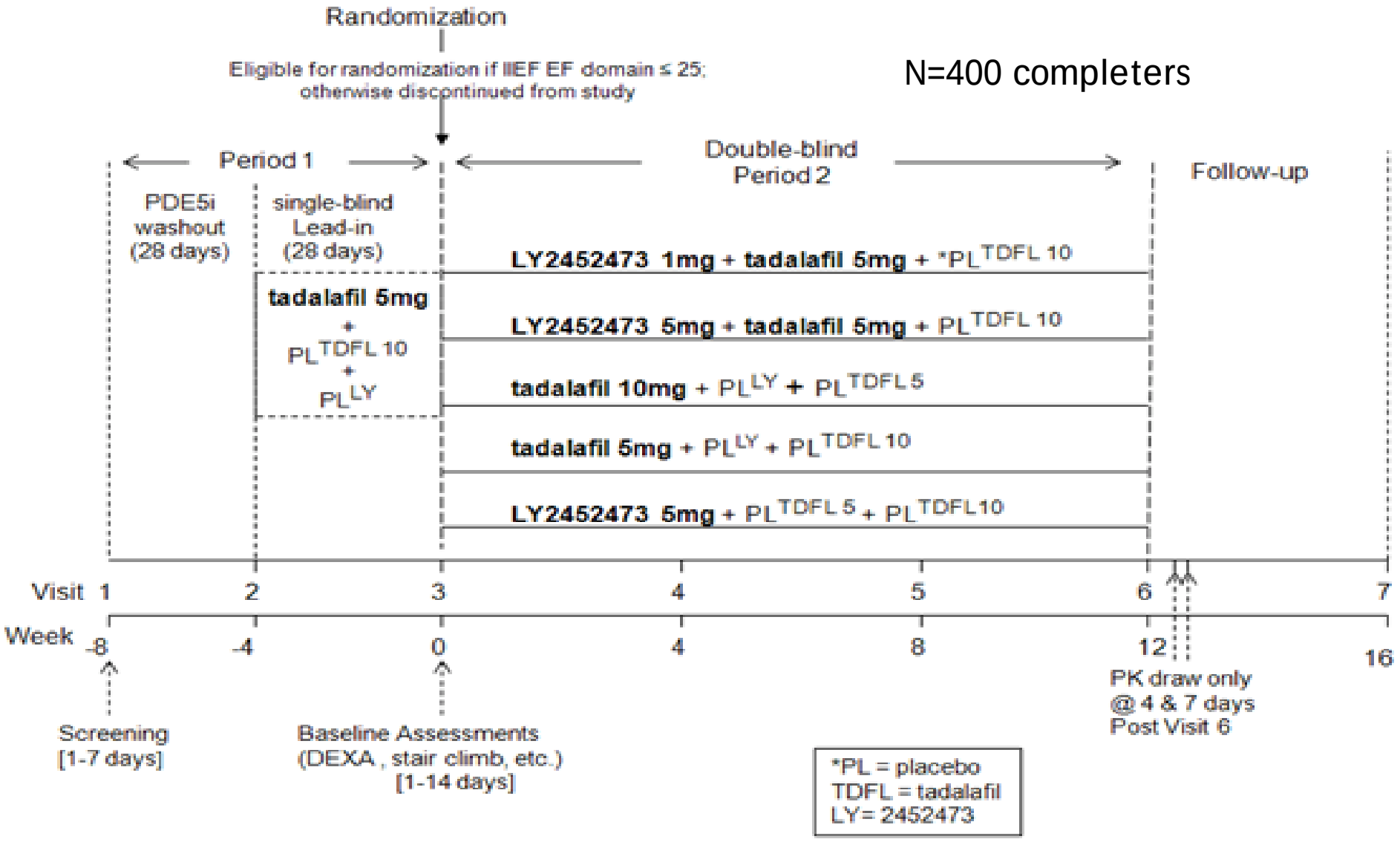
Doses (mg)	CV(EE50) (%)	CV(E_{max}) (%)	Failure rate (%)
1, 3, 5	6.91 (3.11-15.5)	30.2 (13.3-64.4)	0 (0-0.405)
1, 5	6.27 (2.96-14.9)	29.5 (13.8-52.6)	0 (0-0.505)
2, 5	7 (3.12-13)	31.3 (14.2-54.7)	0 (0-0.62)
2, 4	7.04 (2.85-22.4)	32.1 (14-62.9)	0 (0-8.54)
3, 5	6.92 (3-17)	31.2 (13.8-61.4)	0 (0-2.1)

Expected precision and failure rates (and 90% prediction intervals thereof, based on model uncertainty, in parentheses) of exposure-response models for HDL in potential Phase 2 studies

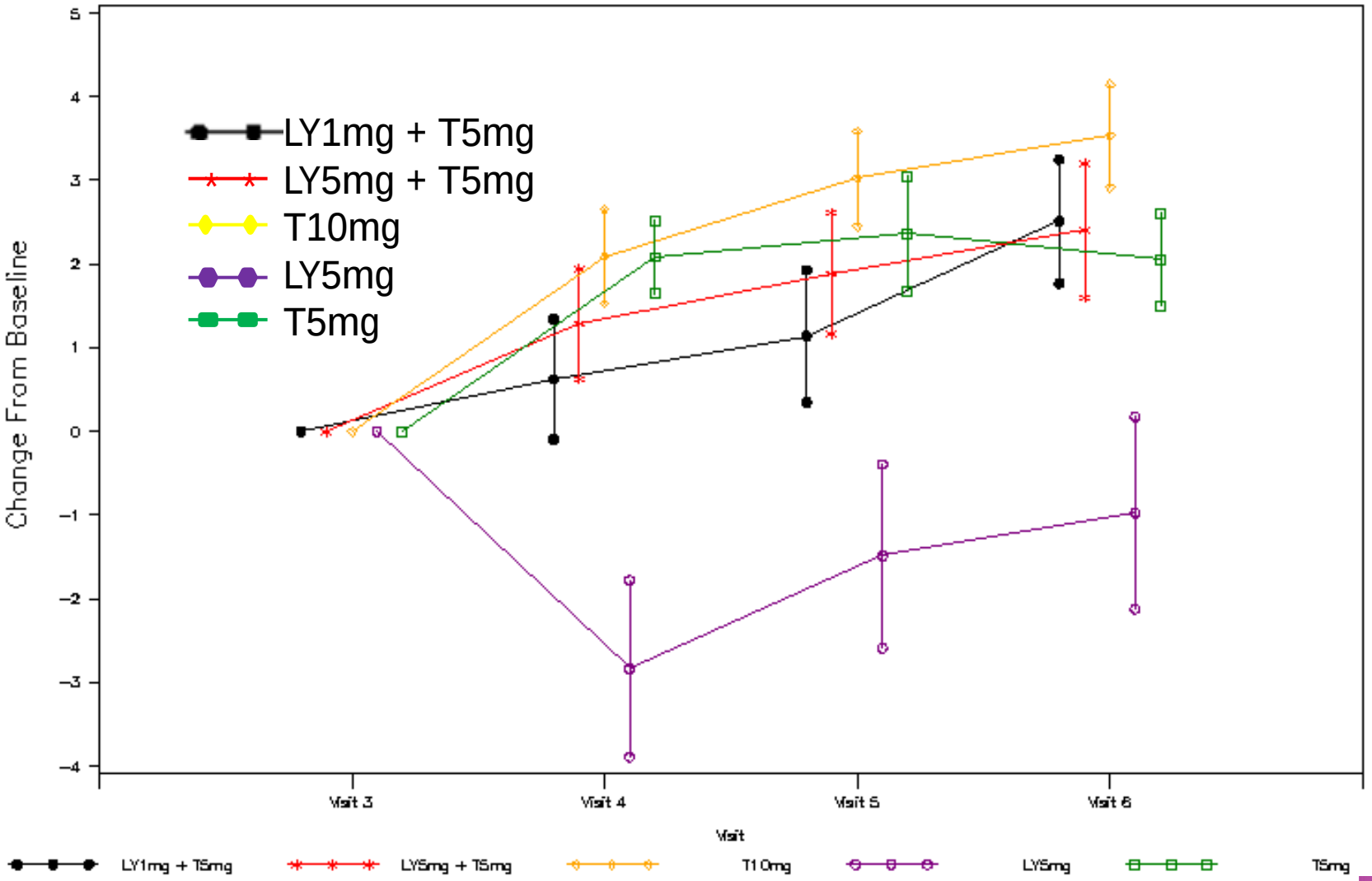
CAN WE LIMIT DOSES IN THE FIXED DOSE COMBINATION STUDY?

- Placebo is not feasible due to PDE5i efficacy
- SARM 1mg and 5 mg in combination with standard of care (tadalafil 5mg)
- SARM alone arm(s) in a non placebo controlled combination study indicate the size of the tadalafil effect
  - SARM + tadalafil = effect
  - Tadalafil alone arm = SARM effect
  - SARM alone arm = tadalafil effect (tadalafil alone is already extremely well characterized)
  - Included per VP request

SARM/TADALAFIL PH 2 STUDY



IIEF ERECTILE FUNCTION DOMAIN



CONCLUSIONS

- Fixed Dose combination Phase 2 studies that explore a full factorial design can involve a large number of arms.
- Modeling and Simulation can help to identify doses with the highest probability of success, and limit the trial to a practical size.
- The trial was able to conclusively demonstrate the lack of efficacy of SARM combined with tadalafil in ED non/partial responders
- Great science and ideas don't always work in patients (most drugs fail…)