

SYSTEMS PHARMACOLOGY MODELING DESCRIBING OSTEOPOROTIC DISEASE PROGRESSION IN A POPULATION OF POSTMENOPAUSAL WOMEN RECEIVING PLACEBO AND/OR ALENDRONATE

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Abstract

Osteoporosis, the most common bone disease, is a major growing public health concern as life expectancy increases. Bisphosphonates, including alendronate, are important medications for treatment and prevention of osteoporosis. The aim is to apply an existing osteoporosis systems pharmacology model beyond the originator dataset to a (new) population of 1609 postmenopausal women who received different doses of alendronate or placebo. We show that, with minor model adaptations, the model accurately describes the observed changes in the available biomarkers. Those changes in biomarkers are the effect of natural disease progression and treatment effect. This example could be useful for scientific use in the osteoporosis therapeutic area (TA) and as an example to build upon for those not working in that TA.

Study population

Table 1. Baseline demographic characteristics of the different treatment arms from the study population.

Characteristic	Placebo	2.5 mg	2.5 mg → placebo	5.0 mg	5.0 mg → placebo
Subjects, n	470	330	133	321	125
Mean age ± SD, years	53.3 ± 3.7	53.3 ± 3.6	53.7 ± 3.5	53.4 ± 3.5	53.7 ± 3.6
Mean BMI ± SD, kg/m ²	25.2 ± 3.6	25.6 ± 3.6	25.3 ± 3.8	25.1 ± 3.7	26.2 ± 3.5
Mean time since menopause ± SD, years	5.7 ± 5.4	6.3 ± 5.9	6.3 ± 6.0	6.5 ± 5.9	6.1 ± 5.5
Mean LS-BMD ± SD, g/cm ²	0.94 ± 0.12	0.93 ± 0.12	0.94 ± 0.14	0.95 ± 0.13	0.96 ± 0.14
Mean TH-BMD ± SD, g/cm ²	0.85 ± 0.11	0.84 ± 0.11	0.83 ± 0.12	0.85 ± 0.12	0.86 ± 0.11
Mean BSAP ± SD (U/L)	11.2 ± 4.4	10.9 ± 3.9	10.1 ± 3.7	10.9 ± 3.7	10.8 ± 4.2
Mean NTX ± SD, nmol bce/mmol cr	88.0 ± 45.0	83.3 ± 46.4	83.6 ± 41.7	86.0 ± 48.2	86.6 ± 47.2

Results

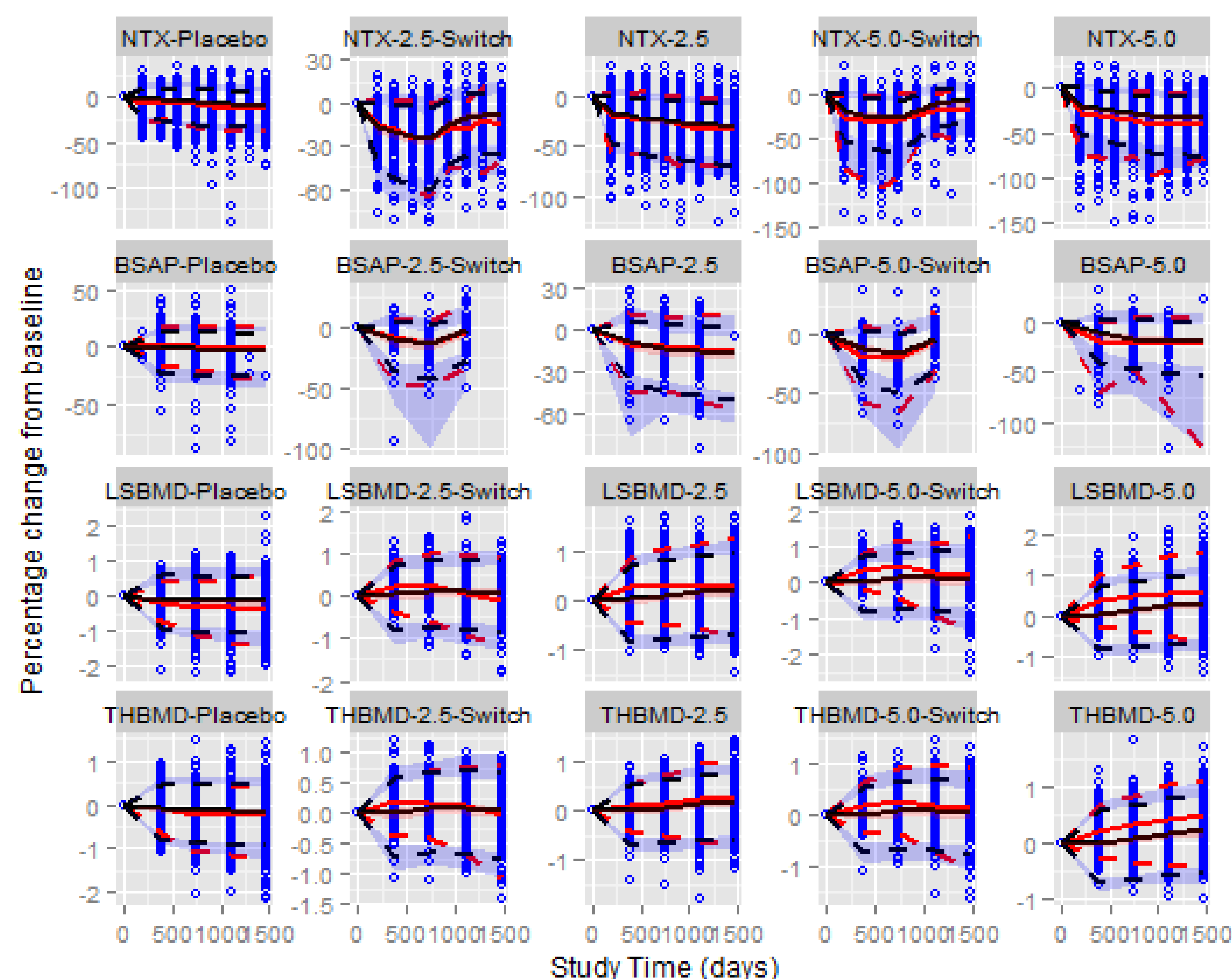


Figure 4. Visual predictive check (VPC) plots. Columns show the different treatment groups, from left to right: placebo, 2 yrs 2.5 mg ALN followed by 2 yrs placebo, 2.5 mg ALN, 2 yrs 5.0 mg ALN followed by 2 yrs placebo, 5.0 mg ALN. Rows correspond to the different markers, from top to bottom: degradation marker NTX, bone formation marker BSAP, LS-BMD and TH-BMD.

Systems pharmacology model

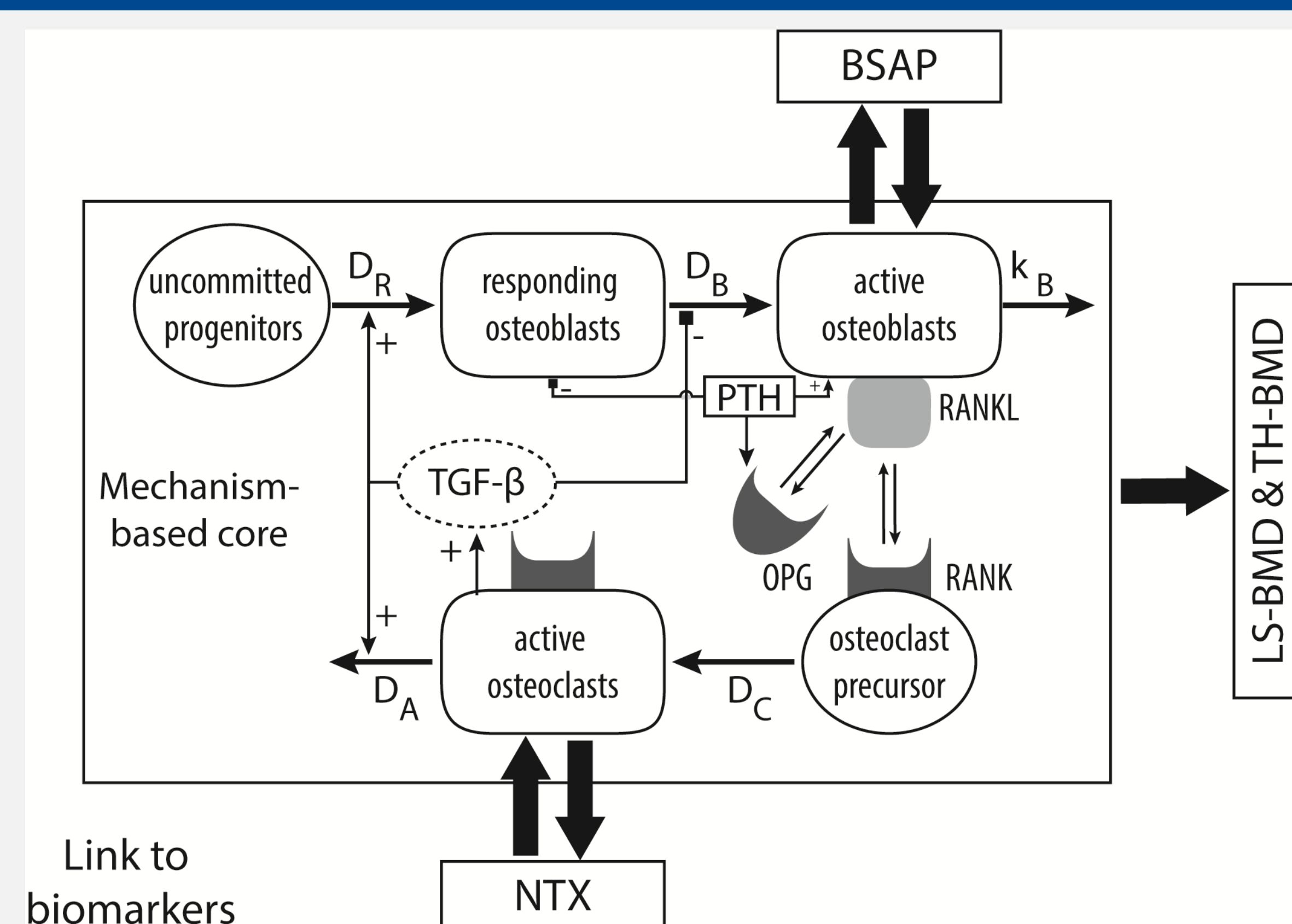


Figure 1. Schematic representation of the mechanism-based disease systems analysis model.

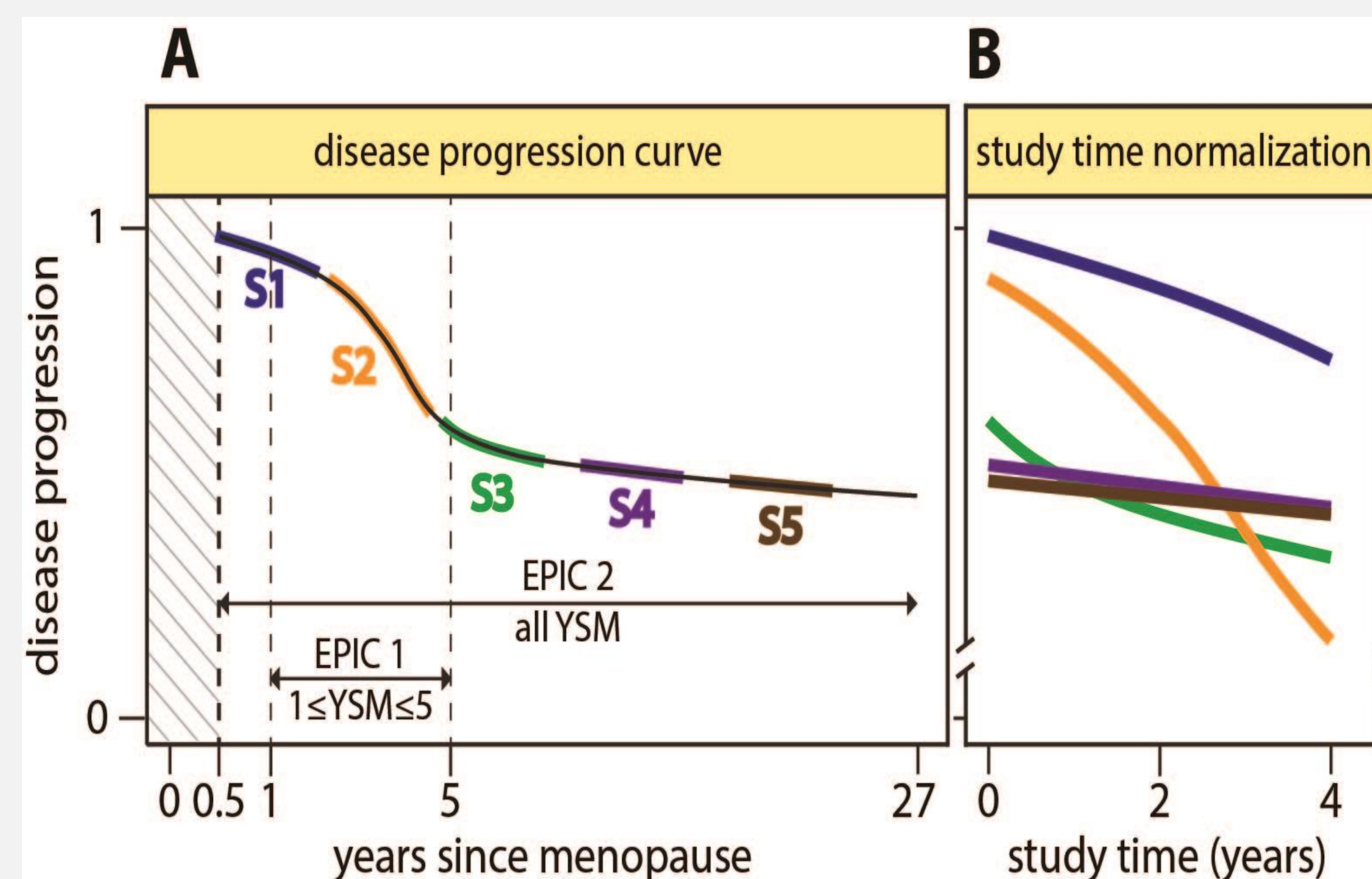


Figure 2. Normalization of individual time scales based on years since menopause (YSM).

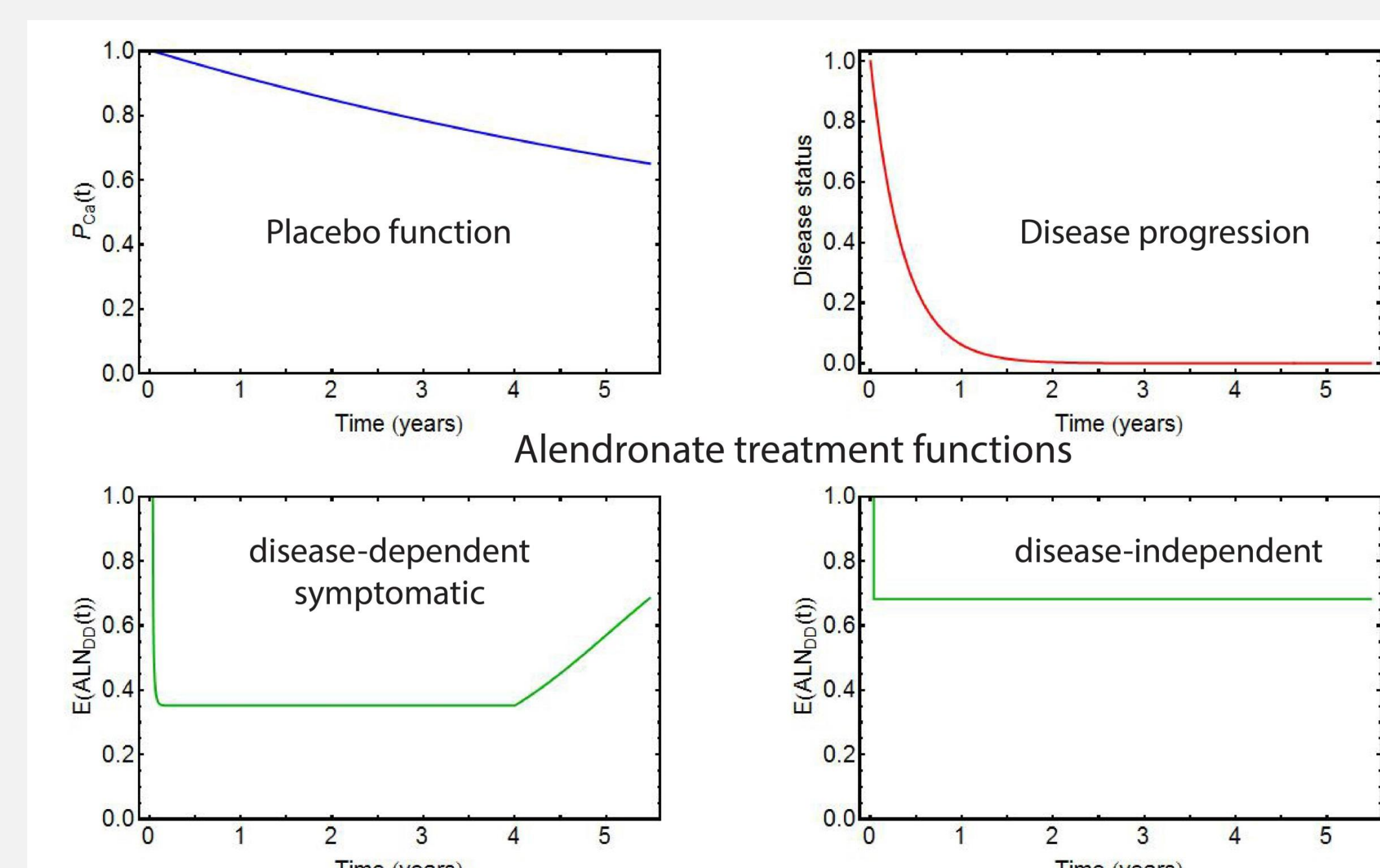


Figure 3. Placebo, disease progression and treatment functions.

References:

- [1] Post et al., J Pharmacokinet Pharmacodyn. 2013;40:143–156
- [2] Ravn et al., Ann Intern Med. 1999;131:935-942