EMEA EFPIA Workshop 19Dec08

Integrating Pgx Early into Drug Development:

PK as a working example

Overview: 4 Sessions over a DAY

Workshop Goal: Collaborative efforts on future paper or guidance

- **Session 1 Set the Scene from EMEA 'Pts to Consider':**
  3 speakers (Experts from Regulatory Authority, Industry, Medical Practice)

- **Session 2 Set the Science** (PK & PGx):
  - ADME Panel (PGx expert)
  - Core Case: Building blocks for Session 3

- **Session 3 Parallel Small Groups on Cases to Design:**
  Design the next drug development phase on the pipeline:
  - Case 1: Phase 1
  - Case 2: Phase 2a
  - Case 3: Standardised Formats
  - Case 4: Phase 2b

- **Session 4**
  Agree areas for consensus & next actions to work together

For Each Case

Workshop Attendees:

- Choose 1 Case (out of 4)
- Become the **Project Team** during the case:
  - Identify who you are and your ***Expertise***
  - Volunteer for ***Project Team Leader*** *(to a team decision)*
  - Volunteer for ***Decision-Table*** to work with Debriefer, in order to generate 1-2 slides for debrief on key messages which arose during the case discussion

Core Case Panel :

- Are the experts who developed the case and will be on the Team as:
  - Project Team Manager (to time session and facilitate process)
  - Data expert
  - Debriefer after Session 3

Case 4 Background
Drug A is in Early Development

Company ABC is developing a **second-in-class Drug A** for a serious, chronic disease, **Diabetes Mellitus Type 2**, for which many patients are insufficiently controlled.

- Drug A is an antagonist which shows no major toxicities in animals at exposures expected to provide >80% receptor occupancy.
- Limiting toxicity is elevated body temperature in dogs.
- A narrow therapeutic margin is expected in patients.

EMEA-EFPIA PGx in PK Workshop

Case 4

Goal:
What does team plan for Phase 2b trial?

Case 4: Plan for Phase 2b

Situation:
Project team has data from Phase 1 & Phase 2a

Target:
Plan for Phase 2b

Given:
- Observed PK variability in Phase 1
- Observed PK variability in Phase 2a

  Data: see next slides (Phase 2a)

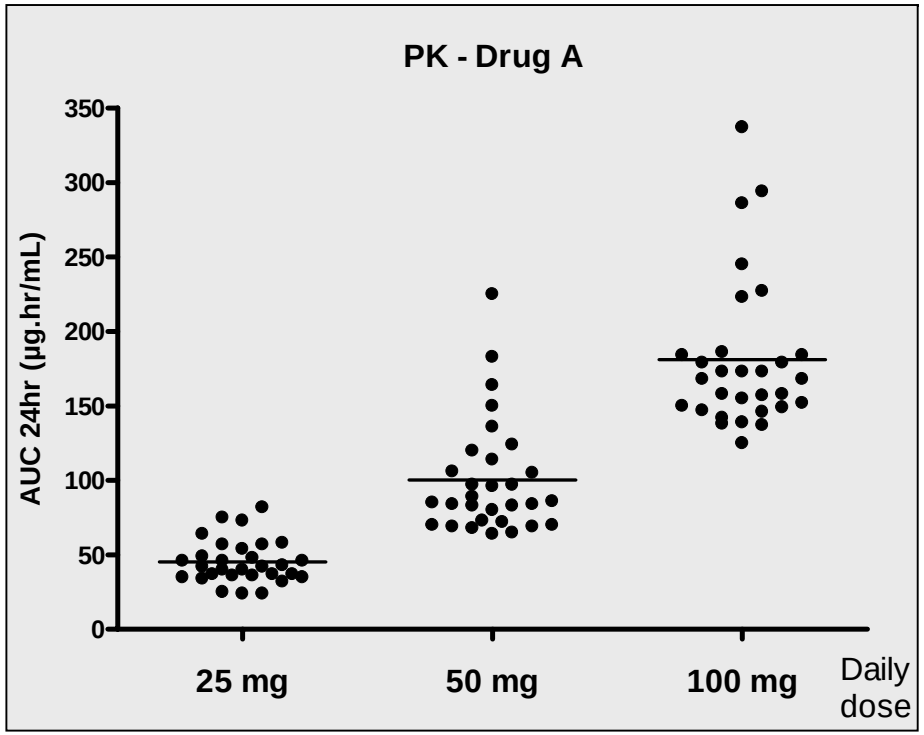
- Phase 2a is dose finding and initial drug effect

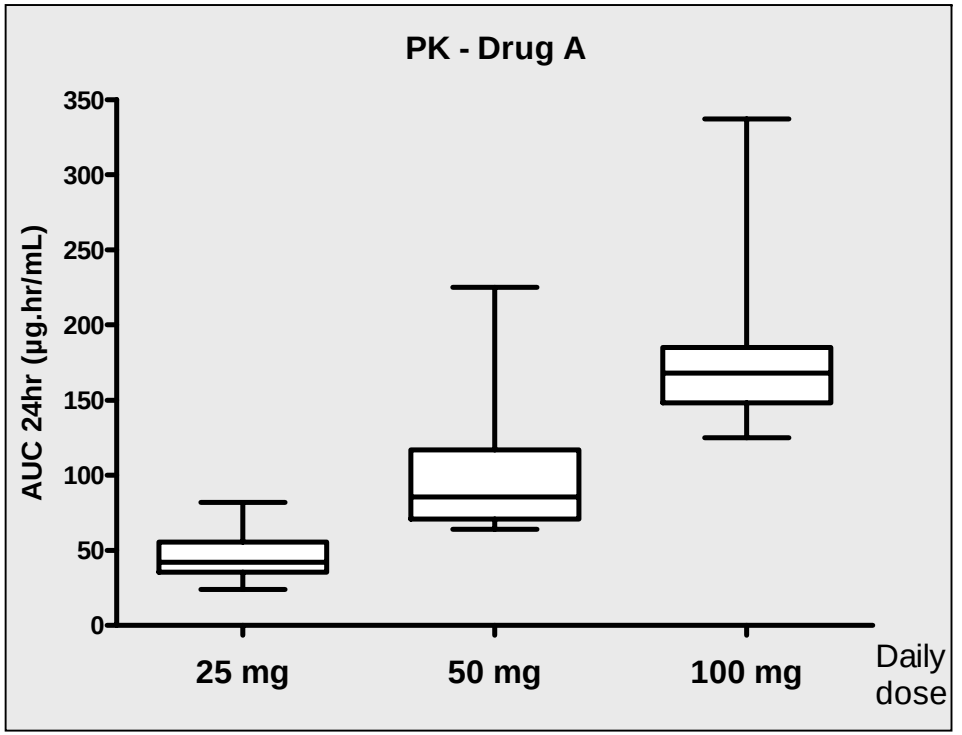
  Drug A Effect is assessed by % glycosylated hemoglobin (HbA1c)

Phase 2A study – PK results

Phase 2A study design:

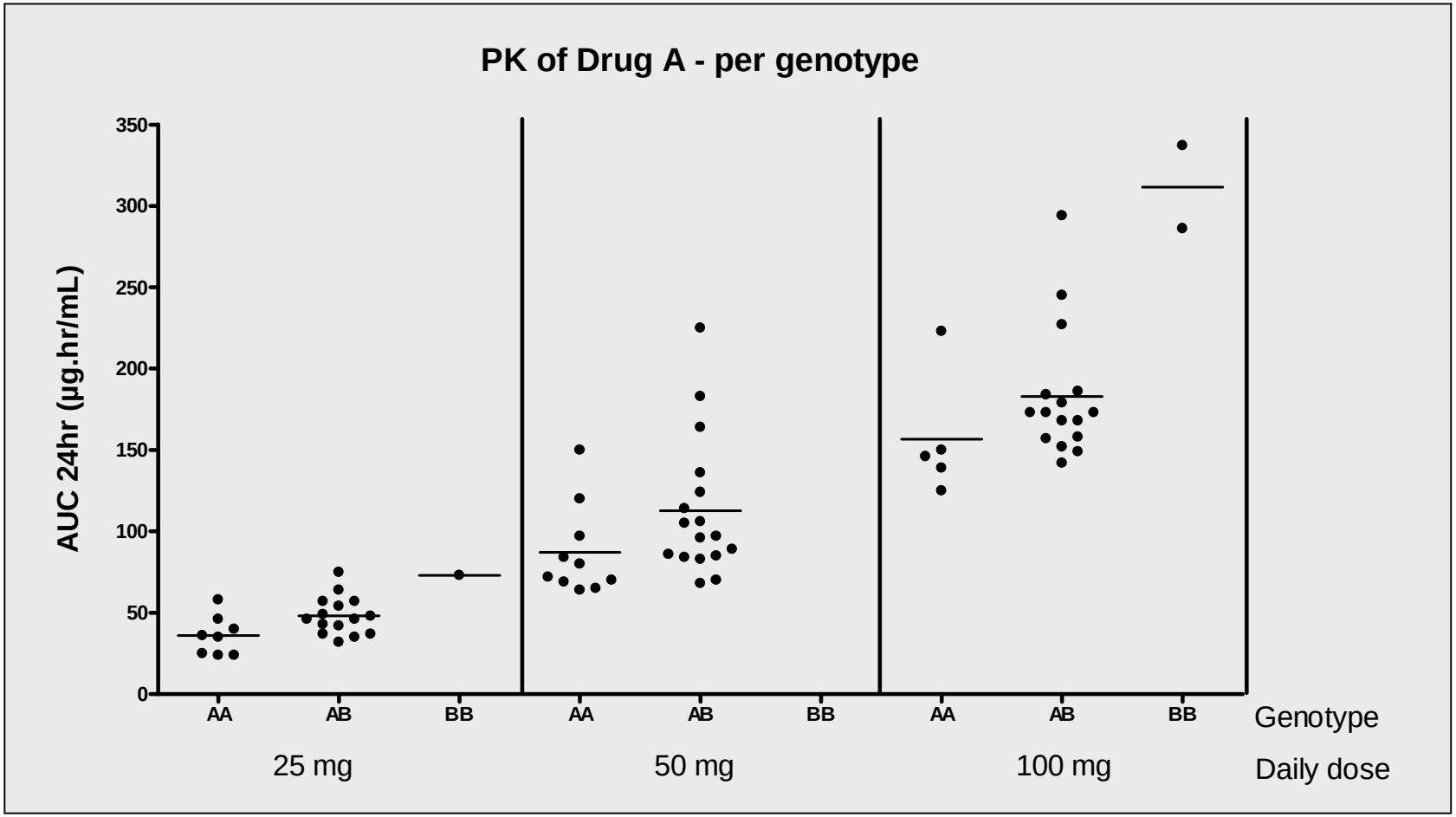
- N = 120 => n = 30 / treatment arm
- Four treatment arms: 0 mg (placebo), 25 mg, 50 mg, 100 mg (daily dose)





Phase 2A study – PK results by CYP2C8 genotype

DNA samples collected for n = 100 subjects (special informed consent)



Case 4: Plan for Phase 2b

Situation:
Project team has data from Phase 1 & Phase 2a

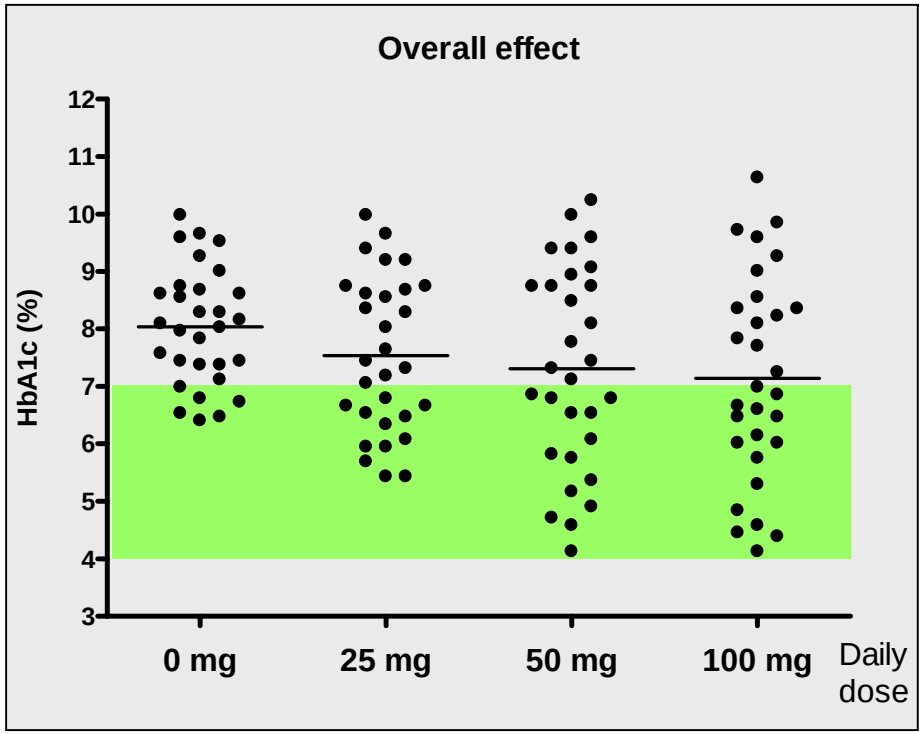
Target:
Plan for Phase 2b

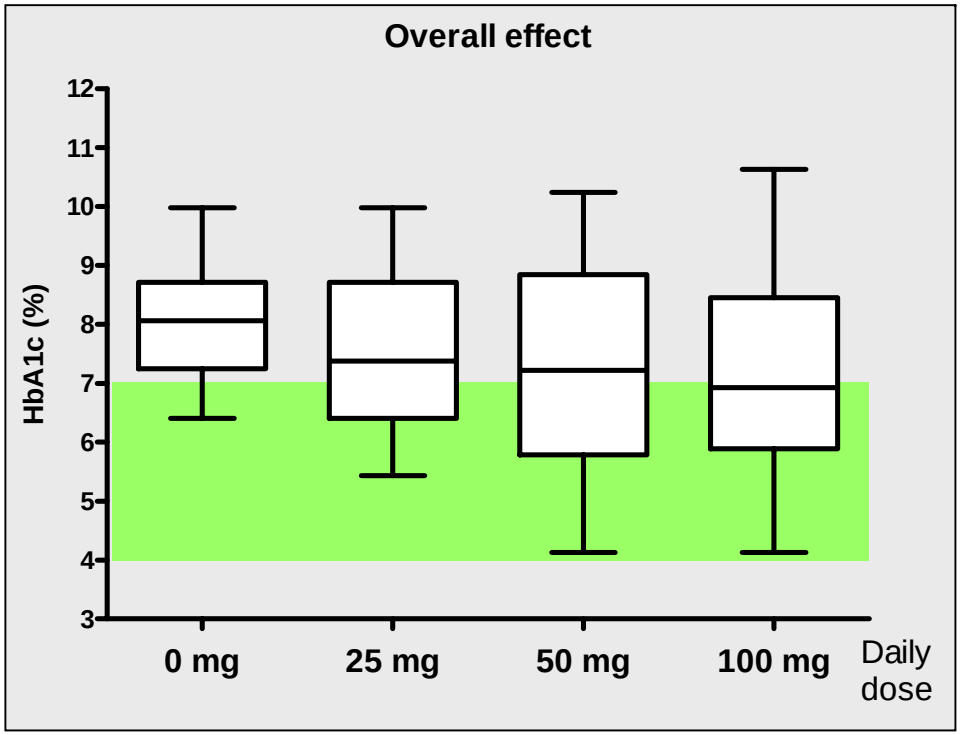
Given:
- Observed PK variability in Phase 1
- Observed PK variability in Phase 2a
- Some effect data from Phase 2a

The key question in drug development:
Does PK variability predict Drug Response ?

Phase 2A study – HbA1c results

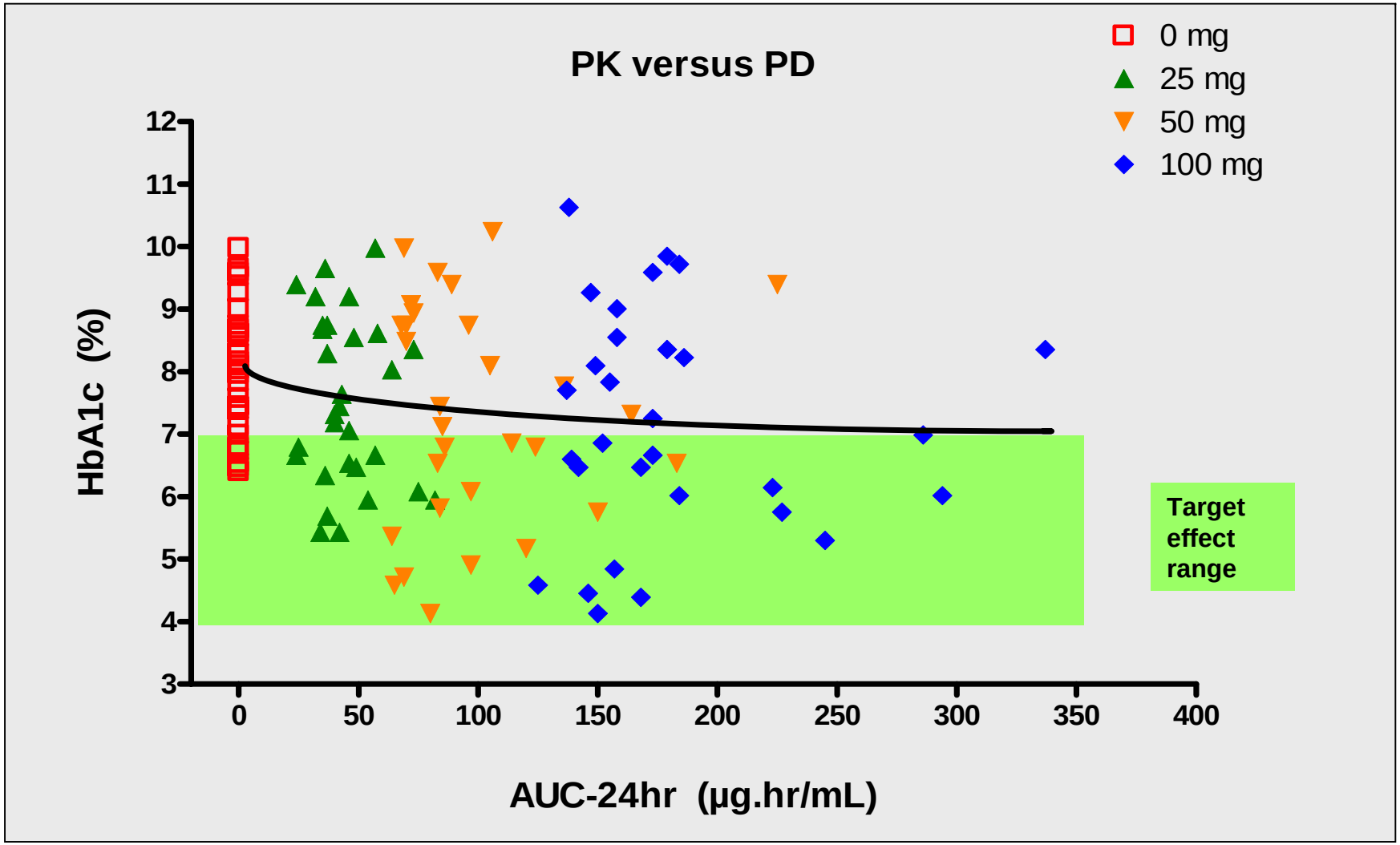
Drug effect assessed by change in % glycosylated hemoglobin (HbA1c)





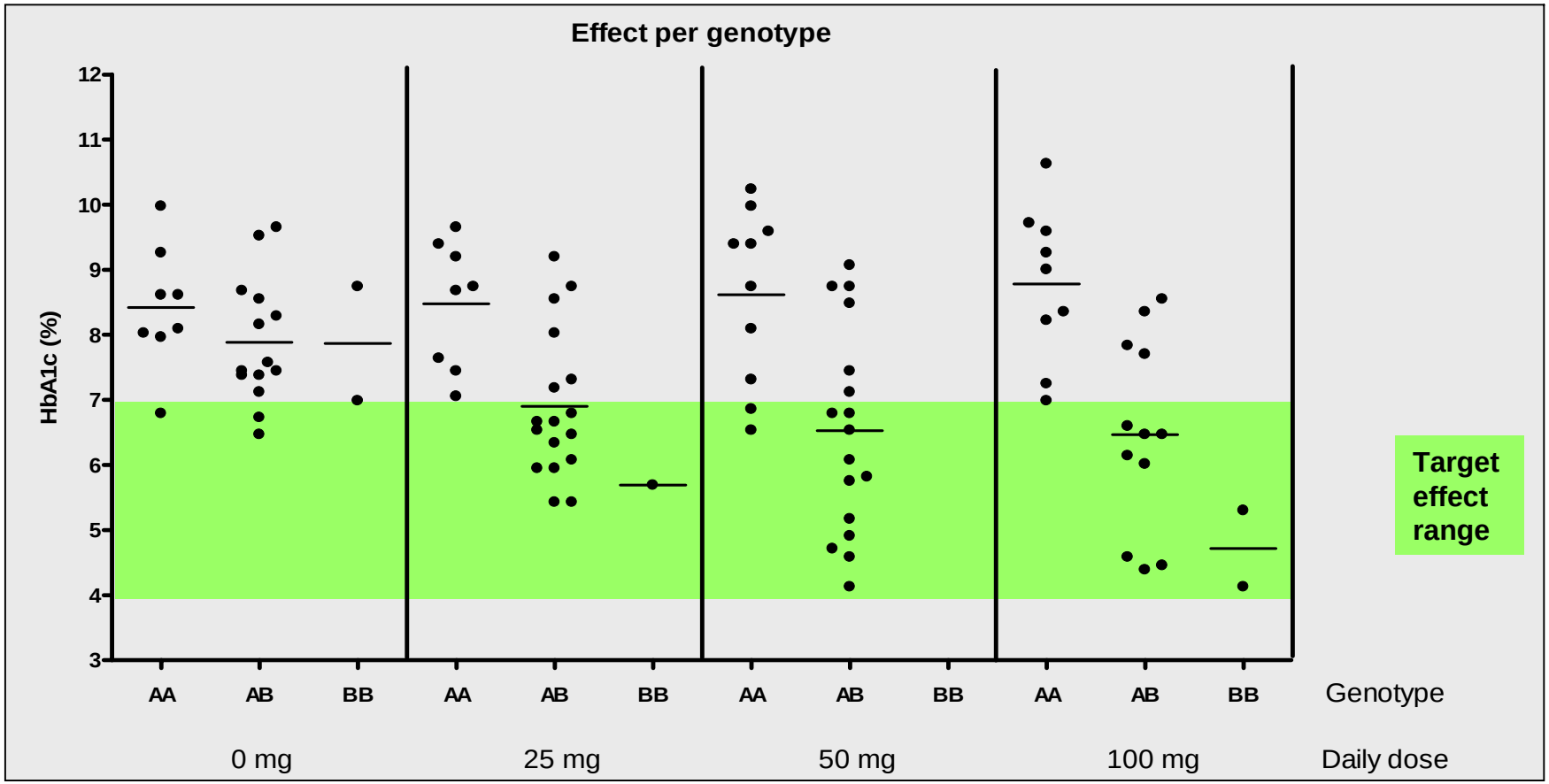
Target effect range HbA1C = 4-7%

Phase 2A study – PK-PD relationship



Phase 2A study – HbA1c results by CYP2C8 genotype

Scenario 1:

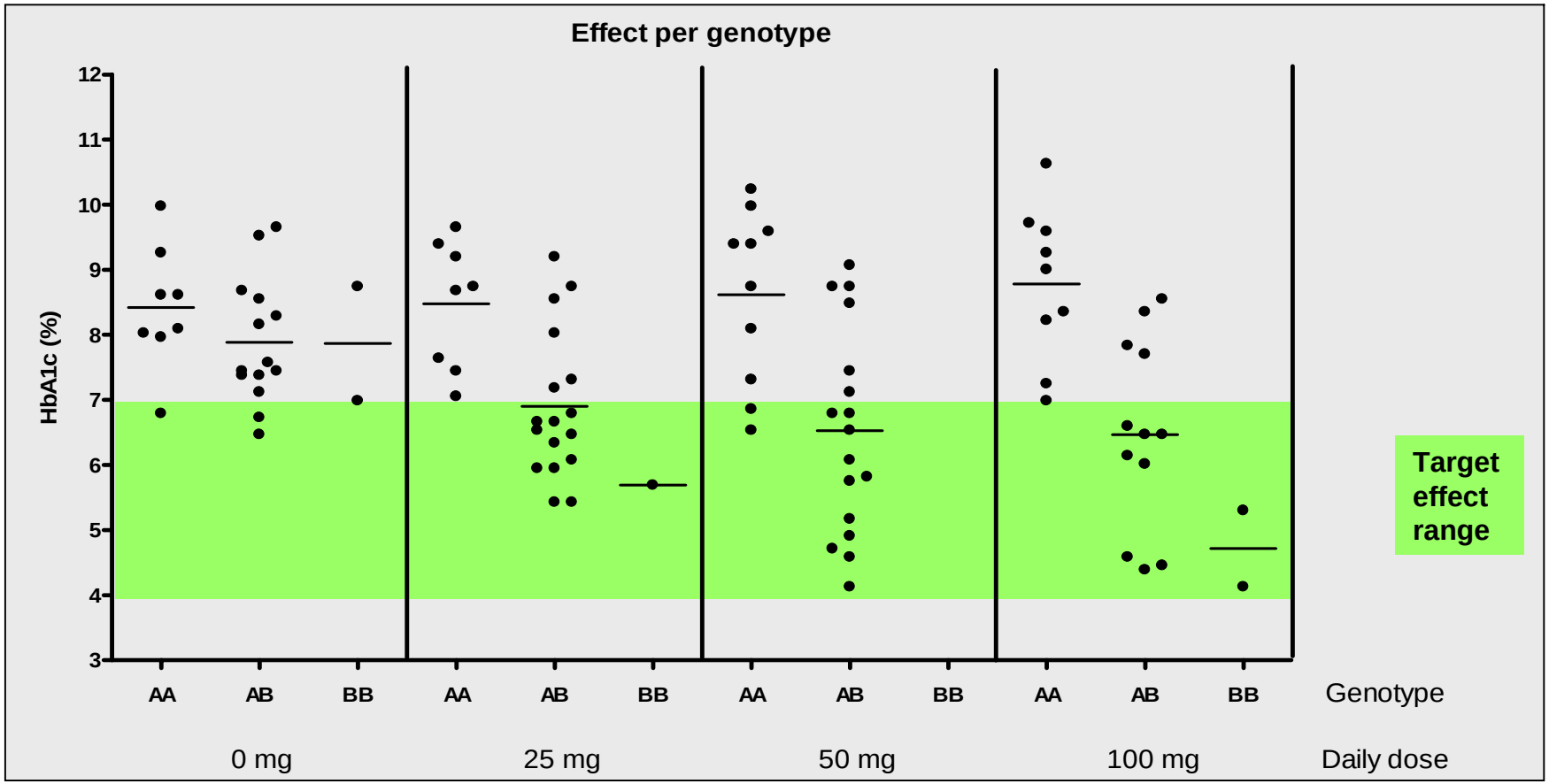


Case 4 – Options for Project Team Decision on its next step: Design of Phase 2B Clinical Trial

Next Team steps > **Scenario: v**	**Do no PGx**	**Only collect DNA**	**Genotype XX pro-spectively in Ph-2B +why**	**Enrich Ph-2B study for specific XX genotype**	**Genotype ADME panel pro-spectively in Ph-2B**	**/**	**Perform exploratory studies (incl. other genes, convert EM to PM by inhibitor)**	**Other proposals**
1: CYP2C8 associates with PK / CYP2C8 associates with effect						/		

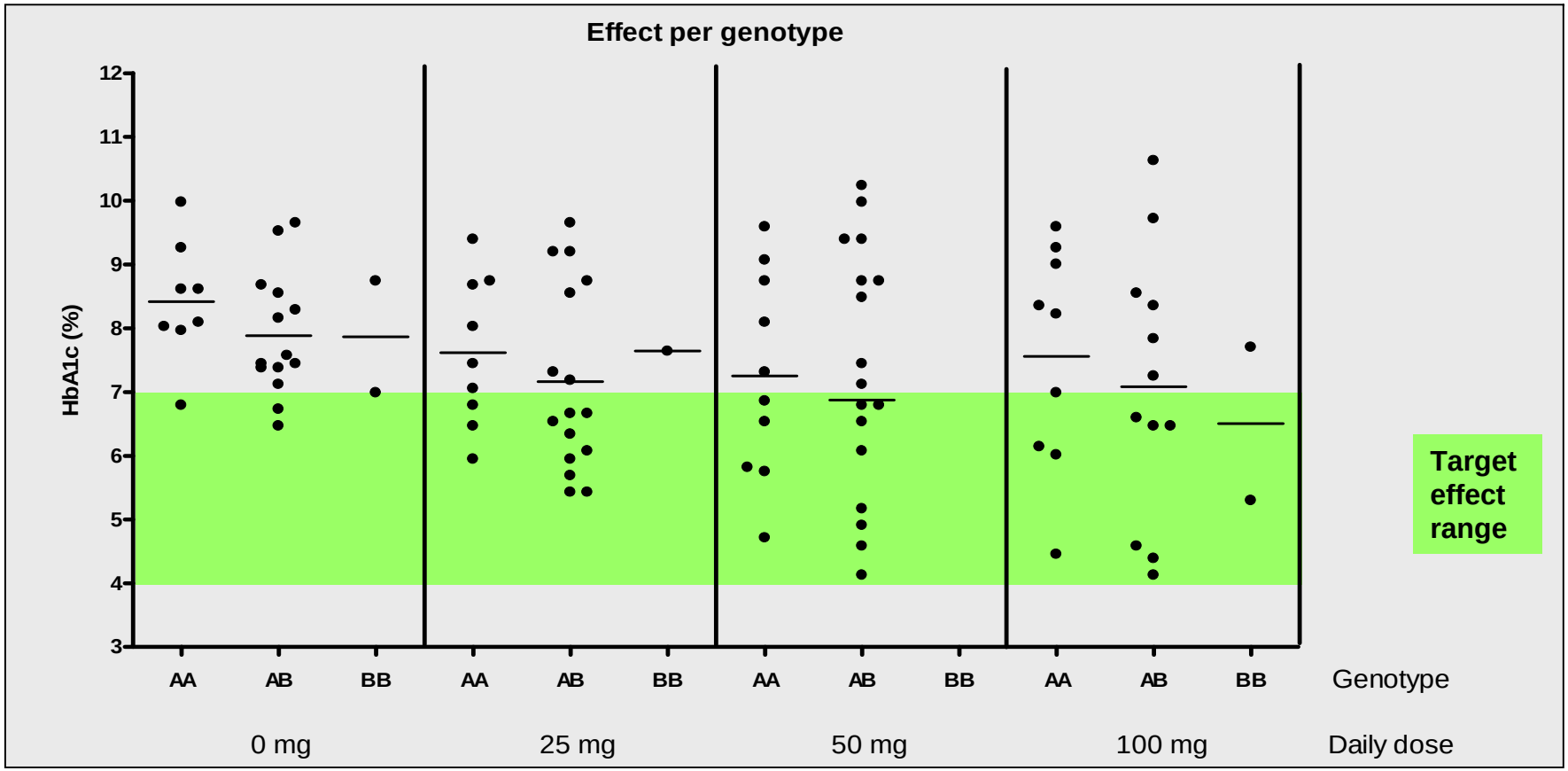
Phase 2A study – HbA1c results by CYP2C8 genotype

Scenario 1: (Ideal or 'dream' situation)



Phase 2A study – HbA1c results by CYP2C8 genotype

Scenario 2: This is actually what the team observed



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2: CYP2C8 associates with PK / CYP2C8 does not associate with effect						/		

Project Team reviews Ph1 and 2a data

Project Team conclusion (scenario 2):

- Variability in effect of drug A on HbA1c
  is partially explained by PK and weakly by CYP2C8

As in real life, emerging data unfolds…

=> Scenario 3

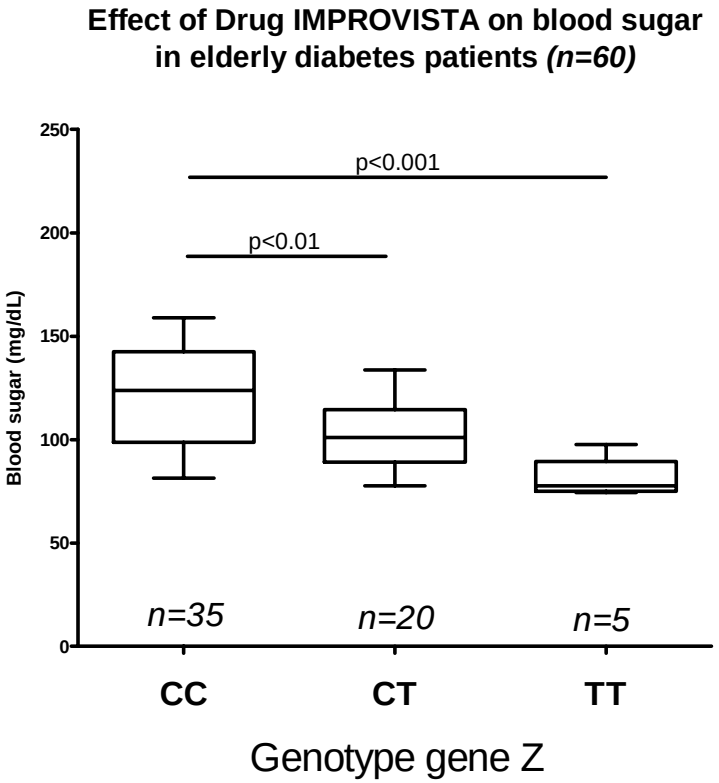
Case 4: Scenario 3 (builds further on Scenario 2)

Results of the following study are published in the public domain literature at the time when the phase 2B study design is discussed.

Anon Y. Mus et al, Lancet 2008

Pharmacogenetic effect of Gene Z genotype on response to IMPROVISTA therapy in diabetes mellitus patients.

- Drug IMPROVISTA is already on the market (first-in-class), and targets the same protein as Drug A.
- The protein encoded by Gene Z is known to be part of the signalling pathway downstream of the target protein, but its exact role in the signalling cascade is not yet understood.
- The functional effect of the examined polymorphism on the protein function is unknown.
- The publication does not report on possible effects of Gene Z genotype on the PK profile of drug IMPROVISTA.



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1: CYP2C8 associates with PK / CYP2C8 associates with effect						Not appl.		
2: CYP2C8 associates with PK / CYP2C8 does not associate with effect						Not appl.		
3: Published Gene Z with efficacy of first-in-class competitor / CYP2C8 does not associate with effect (drug A)								

Case 4: Scenario 4

(builds further on Scenario 3)

As in real life, emerging drug development decisions unfold…

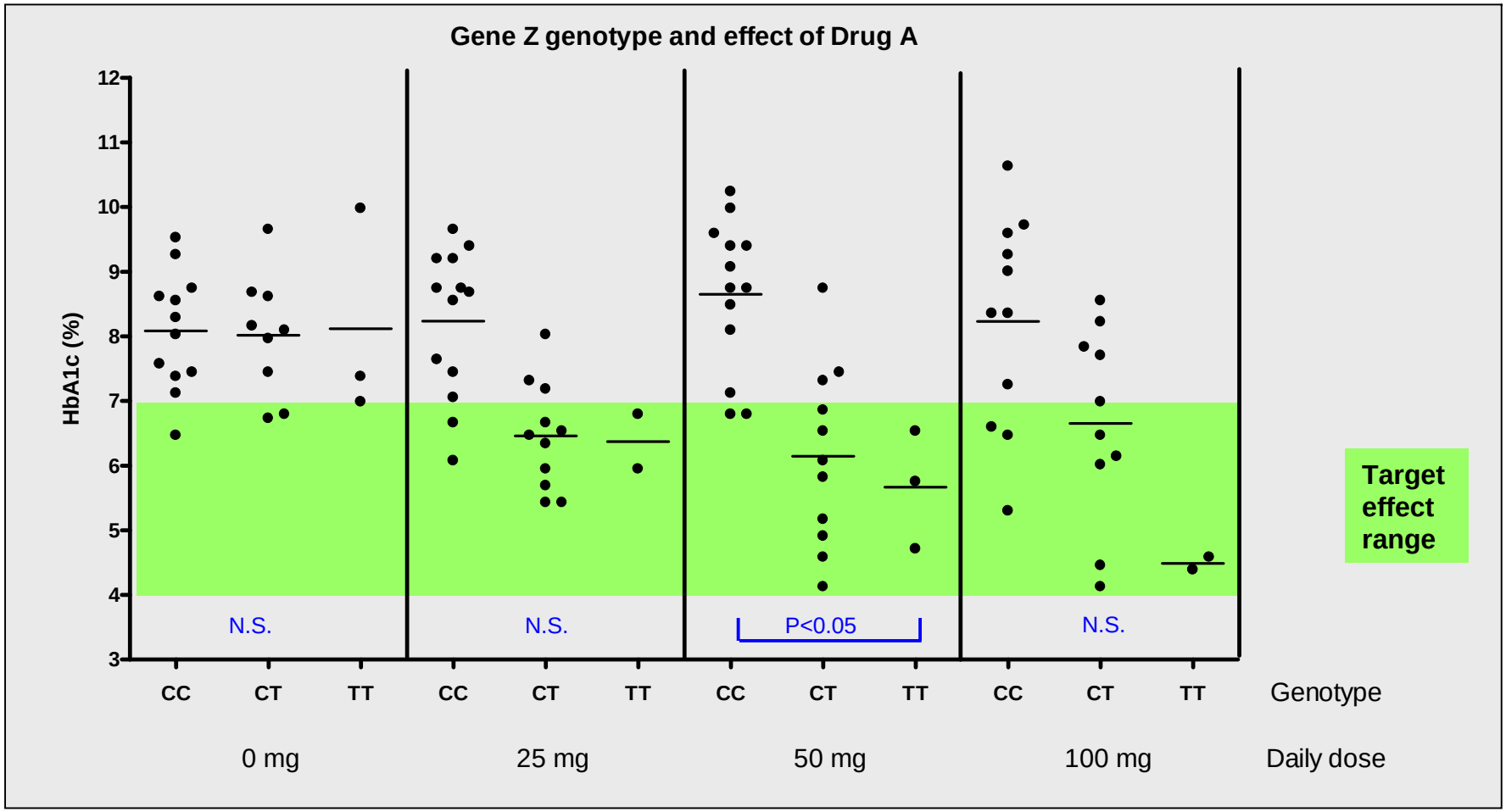
- Executives in the Company decide that the first-in-class drug data (Lancet publication) has enough biological plausibility to also apply for second-in-class Drug A

- As it happens, consented DNA samples from Phase 2A are available to generate Gene Z genotyping data with Drug A (retrospective analysis) within the Company.

Case 4: Scenario 4

(builds further on Scenario 3)

Project Team reviews Phase 2a data with gene Z (retrospective analysis)



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3: Published Gene Z with efficacy of first-in-class competitor / CYP2C8 does not associate with effect drug A								
4: Internal data of Gene Z on Drug A in Ph-2A study confirms literature / CYP2C8 does not associate with effect drug A								