

# EMEA-EFPIA PGx in PK Workshop

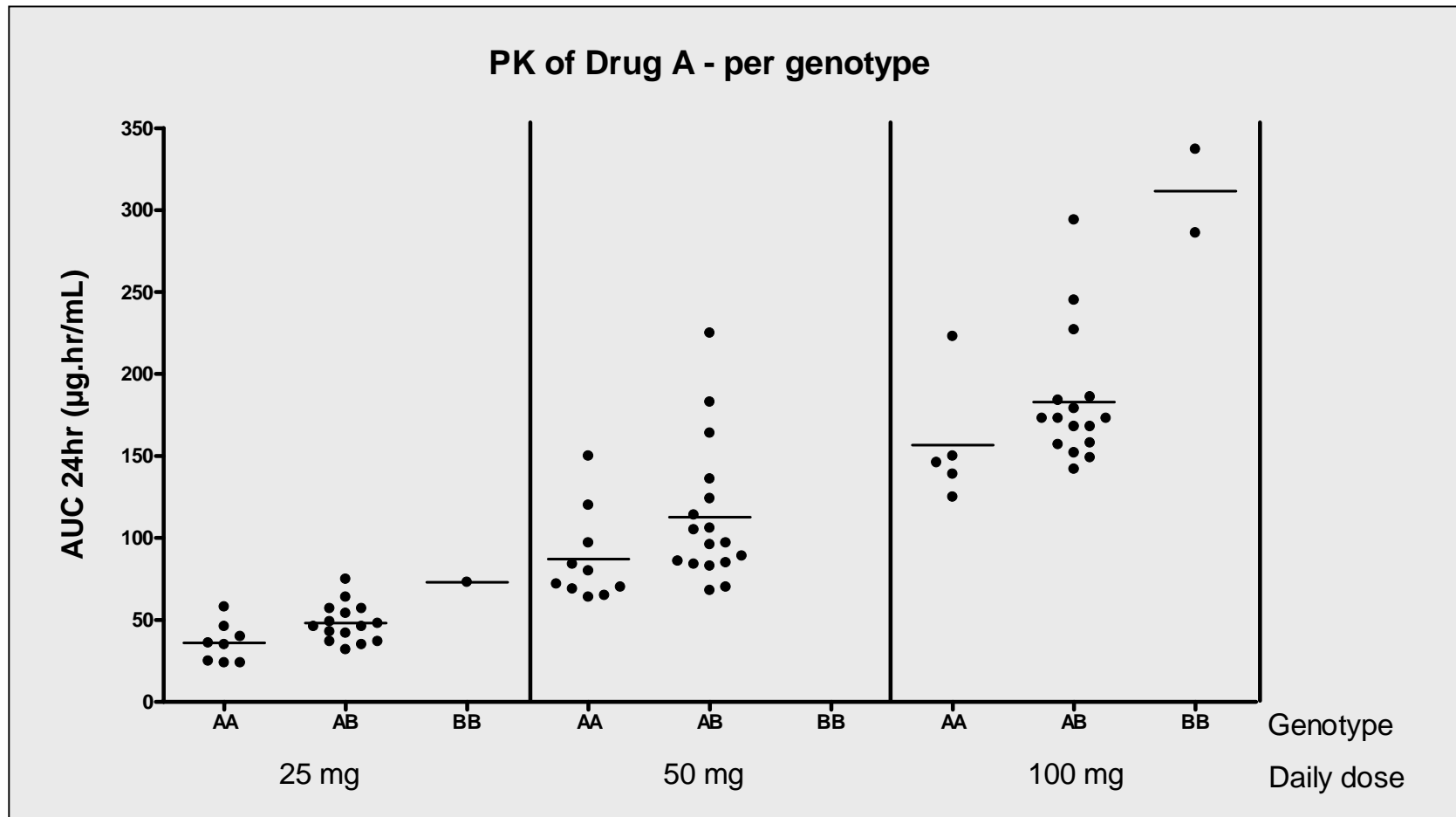
## Case 4

**Goal:**

**What does team plan for Phase 2b trial?**

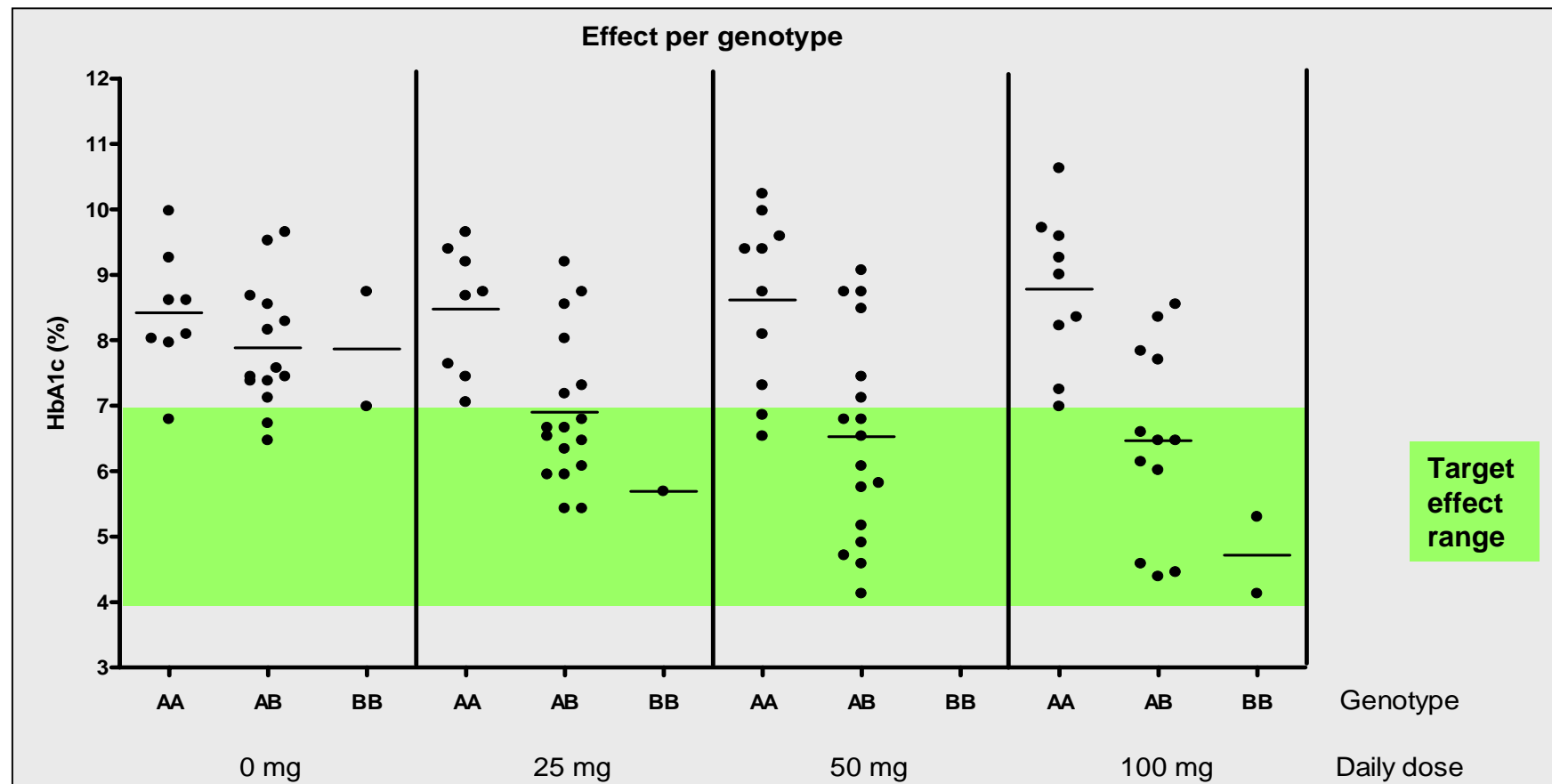
# Phase 2A study – PK results by CYP2C8 genotype

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



# Phase 2A study – HbA1c results by CYP2C8 genotype

## Scenario 1:

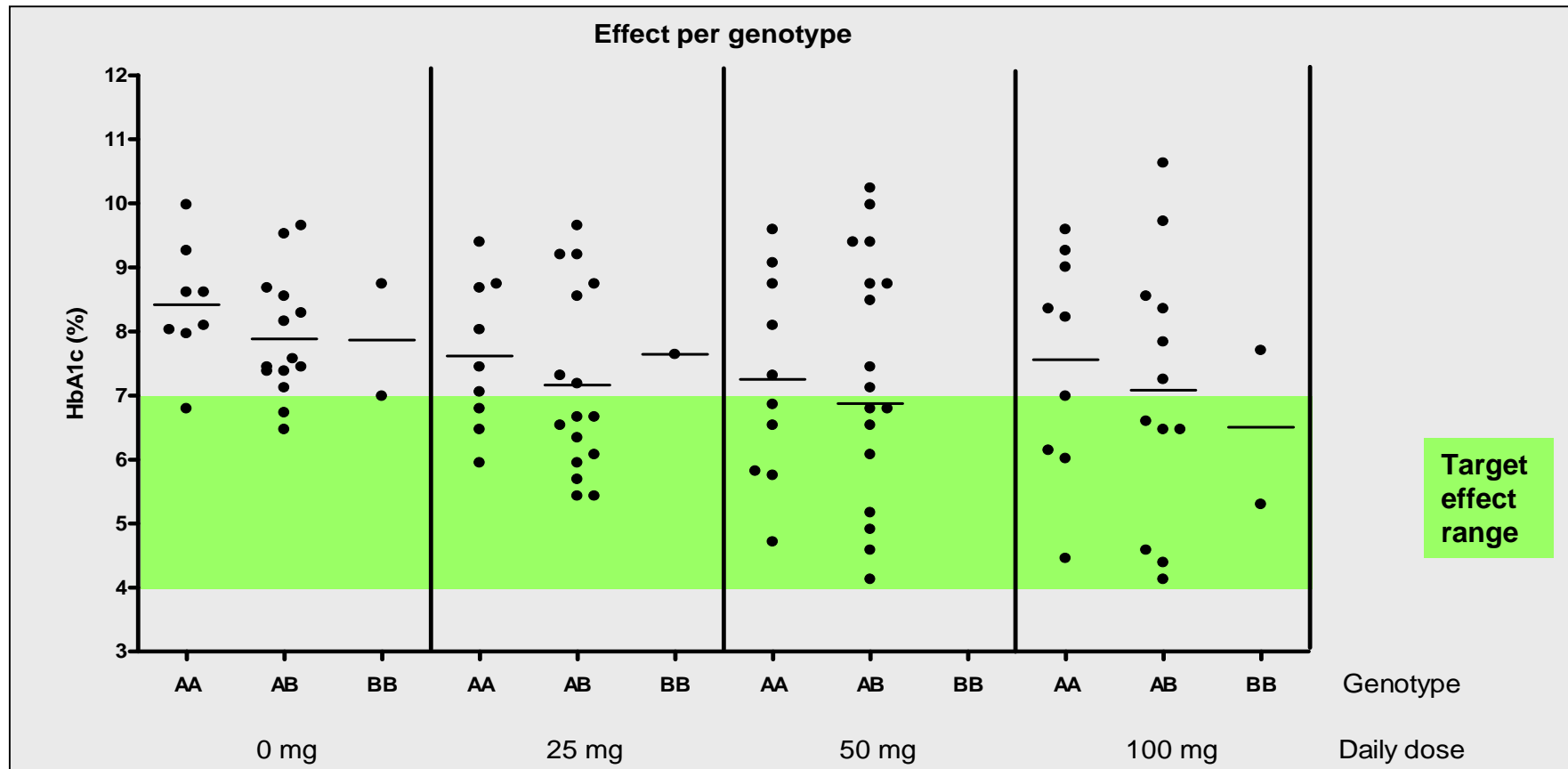


## Case 4 – Options for Project Team Decision on its next step: Design of Phase 2B Clinical Trial

| Next Team steps ><br><br>Scenario: v                                                                                          | Do no PGx | Only collect DNA | Genotype <b>XX</b> prospectively in Ph-2B +why | Enrich Ph-2B study for specific <b>XX</b> genotype | Genotype ADME panel prospectively in Ph-2B | Genotype <b>XX</b> and <b>YY</b> prospectively in Ph-2B | Perform exploratory studies (incl. other genes, convert EM to PM by inhibitor) | Other proposals |
|-------------------------------------------------------------------------------------------------------------------------------|-----------|------------------|------------------------------------------------|----------------------------------------------------|--------------------------------------------|---------------------------------------------------------|--------------------------------------------------------------------------------|-----------------|
| <b>1:</b> CYP2C8 associates with PK / CYP2C8 associates with effect                                                           |           |                  | 7                                              | 4                                                  | 2                                          |                                                         | 2                                                                              | 2               |
| <b>2:</b> CYP2C8 associates with PK / CYP2C8 does not associate with effect                                                   |           |                  |                                                |                                                    |                                            |                                                         |                                                                                |                 |
| <b>3:</b> Published Gene Z with efficacy of first-in-class competitor / CYP2C8 does not associate with effect drug A          |           |                  |                                                |                                                    |                                            |                                                         |                                                                                |                 |
| <b>4:</b> Internal data of Gene Z on Drug A in Ph-2A study confirms literature / CYP2C8 does not associate with effect drug A |           |                  |                                                |                                                    |                                            |                                                         |                                                                                |                 |

# Phase 2A study – HbA1c results by CYP2C8 genotype

Scenario 2: This is actually what the team observed



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

| Next Team steps ><br><br>Scenario: v                                                                                          | Do no PGx | Only collect DNA | Genotype <b>XX</b> prospectively in Ph-2B +why | Enrich Ph-2B study for specific <b>XX</b> genotype | Genotype ADME panel prospectively in Ph-2B | Genotype <b>XX</b> and <b>YY</b> prospectively in Ph-2B | Perform exploratory studies (incl. other genes, convert EM to PM by inhibitor) | Other proposals |
|-------------------------------------------------------------------------------------------------------------------------------|-----------|------------------|------------------------------------------------|----------------------------------------------------|--------------------------------------------|---------------------------------------------------------|--------------------------------------------------------------------------------|-----------------|
| <b>1:</b> CYP2C8 associates with PK / CYP2C8 associates with effect                                                           |           |                  | 7                                              | 4                                                  | 2                                          |                                                         | 2                                                                              | 2               |
| <b>2:</b> CYP2C8 associates with PK / CYP2C8 does not associate with effect                                                   |           | 8                |                                                |                                                    | 1                                          | 1                                                       | 2                                                                              | 3               |
| <b>3:</b> Published Gene Z with efficacy of first-in-class competitor / CYP2C8 does not associate with effect drug A          |           |                  |                                                |                                                    |                                            |                                                         |                                                                                |                 |
| <b>4:</b> Internal data of Gene Z on Drug A in Ph-2A study confirms literature / CYP2C8 does not associate with effect drug A |           |                  |                                                |                                                    |                                            |                                                         |                                                                                |                 |

## Case 4: Scenario 3

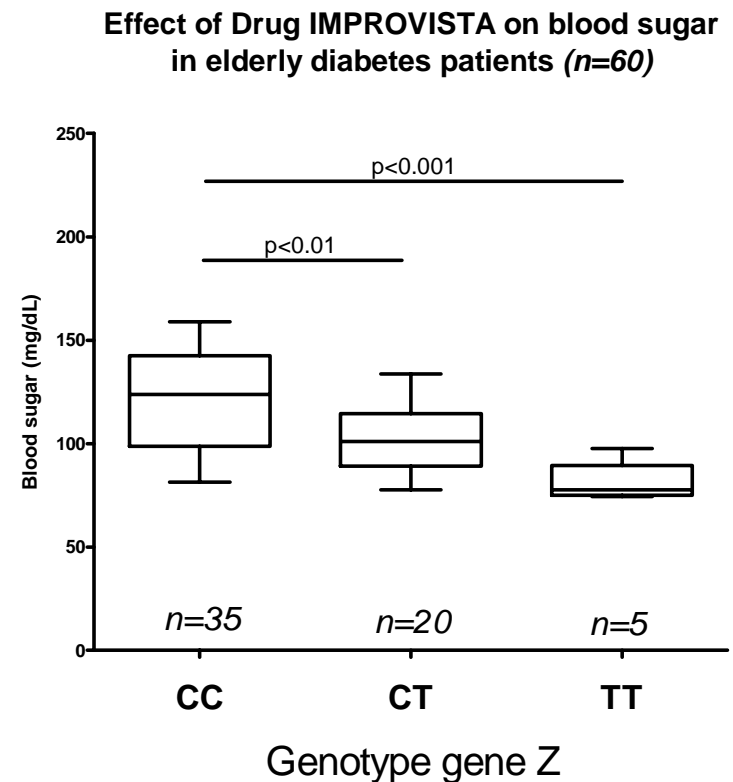
(builds further on Scenario 2)

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.



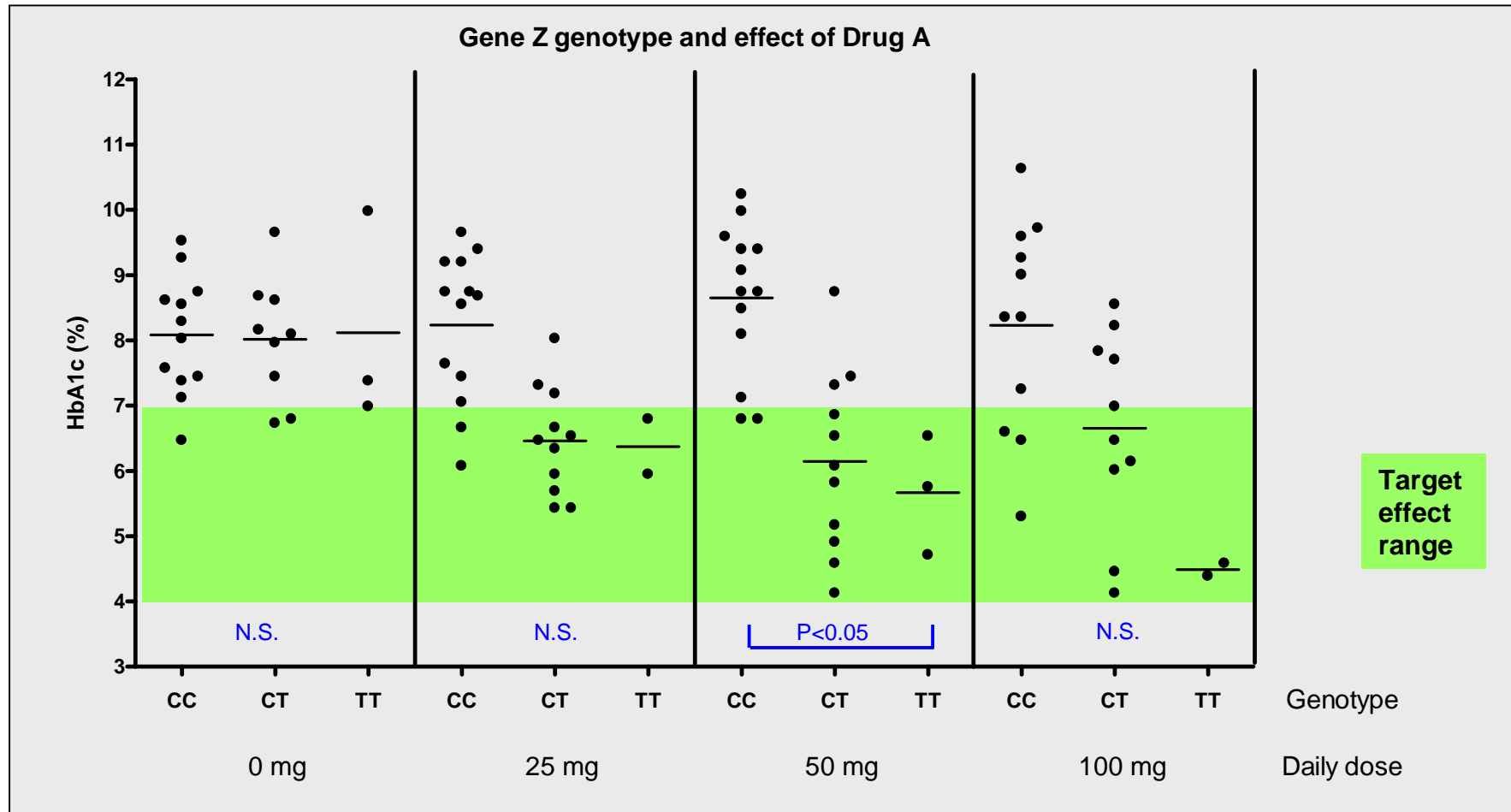
## Case 4 – Options for Project Team Decision on its next step: Design of Phase 2B Clinical Trial

| Next Team steps ><br><br>Scenario: v                                                                                          | Do no PGx | Only collect DNA | Genotype <b>XX</b> prospectively in Ph-2B +why | Enrich Ph-2B study for specific <b>XX</b> genotype | Genotype ADME panel prospectively in Ph-2B | Genotype <b>XX</b> and <b>YY</b> prospectively in Ph-2B | Perform exploratory studies (incl. other genes, convert EM to PM by inhibitor) | Other proposals |
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| <b>2:</b> CYP2C8 associates with PK / CYP2C8 does not associate with effect                                                   |           | 8                |                                                |                                                    | 1                                          | 1                                                       | 2                                                                              | 3               |
| <b>3:</b> Published Gene Z with efficacy of first-in-class competitor / CYP2C8 does not associate with effect drug A          |           | 5                |                                                |                                                    |                                            | 3                                                       | 5                                                                              | 3               |
| <b>4:</b> Internal data of Gene Z on Drug A in Ph-2A study confirms literature / CYP2C8 does not associate with effect drug A |           |                  |                                                |                                                    |                                            |                                                         |                                                                                |                 |

## Case 4: Scenario 4

(builds further on Scenario 3)

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



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

| Next Team<br>steps ><br><br>Scenario: v                                                                                                      | Do no<br>PGx | Only<br>collect<br>DNA | Genotype<br><b>XX</b><br>pro-<br>spectivel<br>y in Ph-<br>2B<br>+why | Enrich Ph-<br>2B study<br>for specific<br><b>XX</b><br>genotype | Genotype<br>ADME<br>panel<br>pro-<br>spectively<br>in Ph-2B | Genotype<br><b>XX</b> and <b>YY</b><br>prospective<br>ly in Ph-2B | Perform<br>exploratory<br>studies (incl.<br>other genes,<br>convert EM to<br>PM by inhibitor) | Other<br>proposals |
|----------------------------------------------------------------------------------------------------------------------------------------------|--------------|------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------|
| <b>1:</b> CYP2C8<br>associates with PK /<br>CYP2C8 associates with<br>effect                                                                 |              |                        | 7                                                                    | 4                                                               | 2                                                           |                                                                   | 2                                                                                             | 2                  |
| <b>2:</b> CYP2C8<br>associates with PK /<br>CYP2C8 does not<br>associate with effect                                                         |              | 8                      |                                                                      |                                                                 | 1                                                           | 1                                                                 | 2                                                                                             | 3                  |
| <b>3:</b> Published Gene Z<br>with efficacy of first-in-<br>class competitor /<br>CYP2C8 does not<br>associate with effect<br>drug A         |              | 5                      |                                                                      |                                                                 |                                                             | 3                                                                 | 5                                                                                             | 3                  |
| <b>4:</b> Internal data of Gene<br>Z on Drug A in Ph-2A<br>study confirms literature /<br>CYP2C8 does not<br>associate with effect<br>drug A |              | 1                      | 8                                                                    |                                                                 |                                                             | 2                                                                 |                                                                                               | 7                  |

# Conclusions

- Decision depends on context and data available from earlier studies
- DNA should always be collected as minimum for all scenarios
  - Complete agreement from participants
  - Vital in change of view from Scen. 3 to 4
- Pharmacogenetics should not be considered in isolation
  - Effect of age, toxicity data, different efficacy markers