Cas particulier des associations de produits médicamenteux

Paul Chevalier

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Overview of the presentation

1. Introduction

- Main recommendations from the draft FDA guidance (Jan. 05)

2. An example

- Results of the 1-month TK on the combination of two New Molecules Entities (NMEs) in mice and monkeys
- Results of the FIM

3. Consequences of preclinical safety / FIM results

- Plasma exposures in man vs. mouse and monkey at NOAEL
- What are the Consequences for the Multiple-Dose Study in Healthy Volunteers?

4. Action Plan to Support Multiple-Dose in Healthy Volunteers

Nonclinical safety evaluation of drug combinations

Drug combinations may involve:

- Previously marketed drugs
- One or more new molecular entities (NME) and one or more previously marketed drugs
- More than one NME

Administration of a drug combination can be done as:

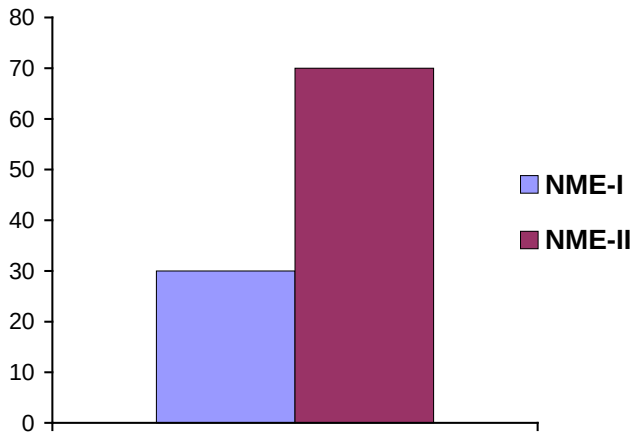
- A fixed-dose combination products (single dosage form)
- A co-packaged product (with appropriate labeling)
- An adjunctive therapy

FDA guidance (draft, Jan. 05) applied to two NMEs

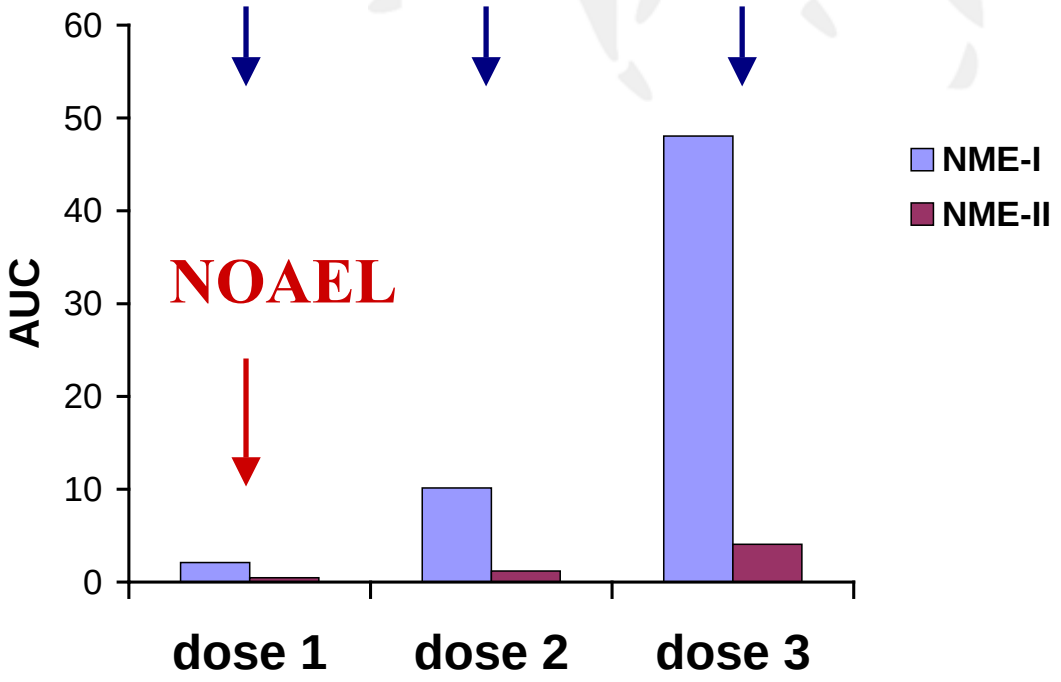
- If the two drugs are proposed to be marketed together only, it may be sufficient to conduct toxicology studies only on the combination
  - However, non clinical studies conducted on each NME alone can be invaluable should it become important to alter the clinical regimen from what is initially proposed or studied
- FDA recommends that the sponsor conduct non clinical studies on each NME to evaluate the safety of a combination of NMEs
  - Standard battery of nonclinical studies (genetic toxicology, pharmacology, safety pharmacology, PK/ADME, general toxicity, reproductive and developmental toxicity, carcinogenicity)
- Depending on the duration of the proposed therapy, a bridging study of up to 90 days should be conducted with the combination
  - Because the drug ratio may change during drug development, it is important to design the toxicity studies to provide adequate safety margins of safety for future clinical studies
- PK/ADME and Toxicokinetics to assess interaction

Safety Pharmacology of the combination
4-week toxicity study in mice

Suspension
NME-I / NME-II ratio
30 / 70



Exposure
NME-I / NME-II ratios
82 / 18 89 / 11 92 / 8



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Safety Pharmacology of the combination
4-week toxicity study in monkey

Suspension
NME-I / NME-II ratio
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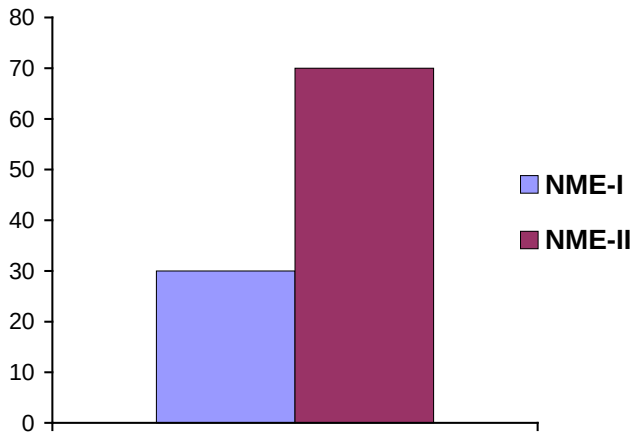
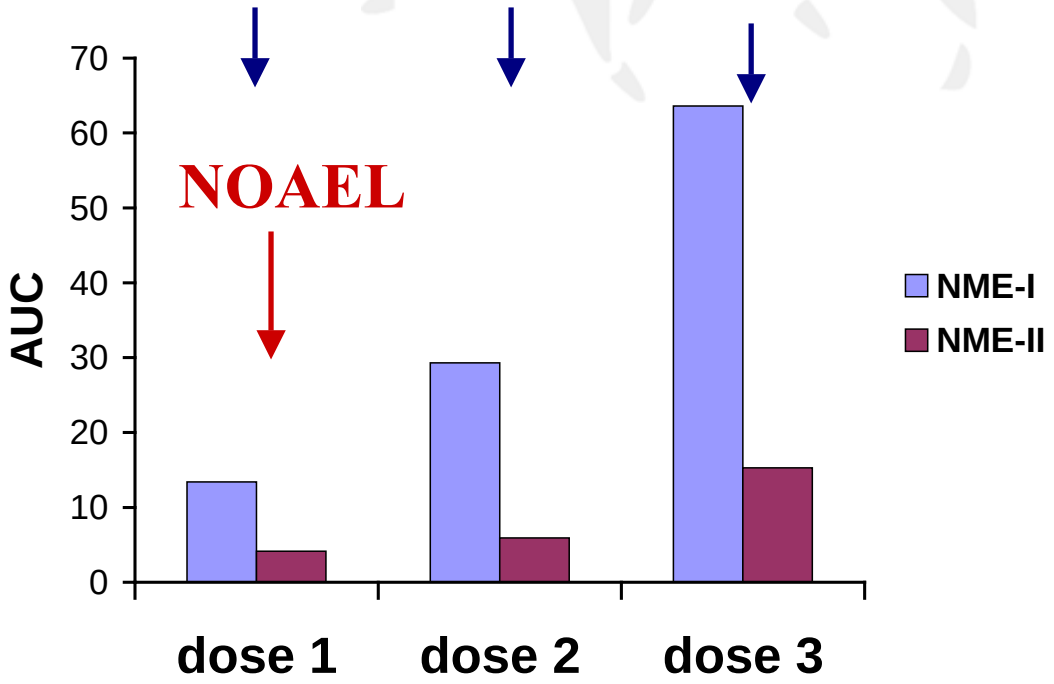


Exposure
NME-I / NME-II ratios
76 / 24 83 / 17 81 / 19



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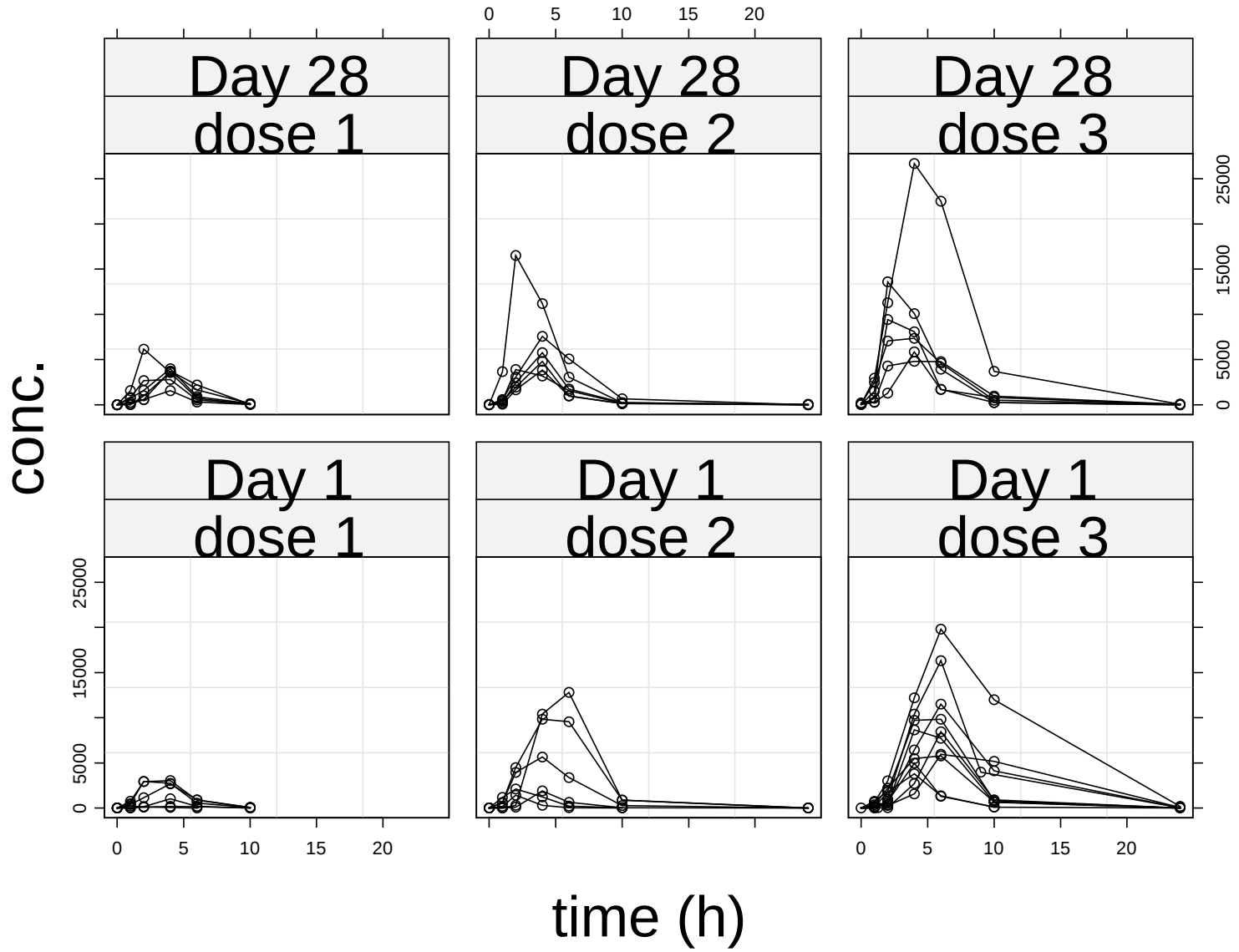
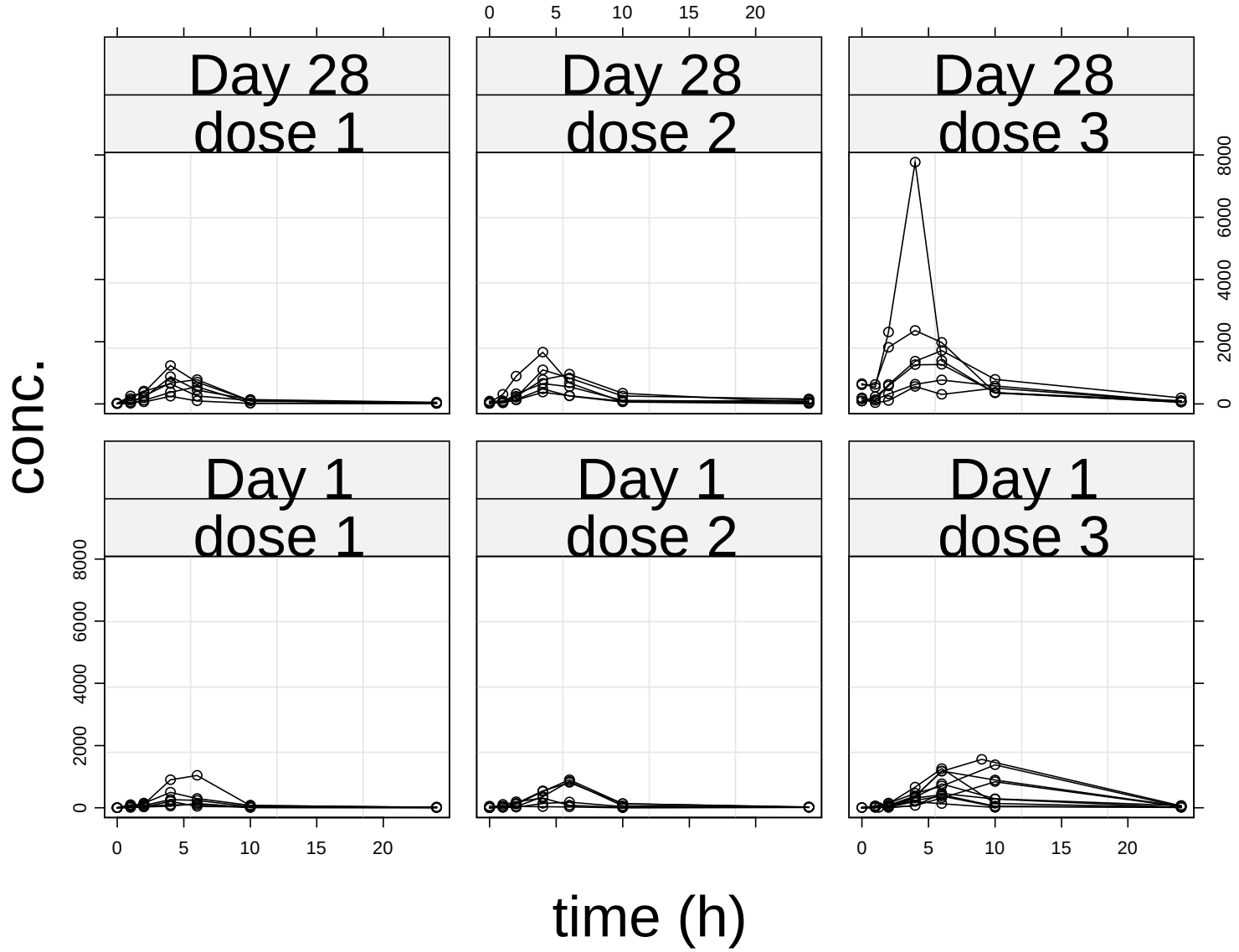
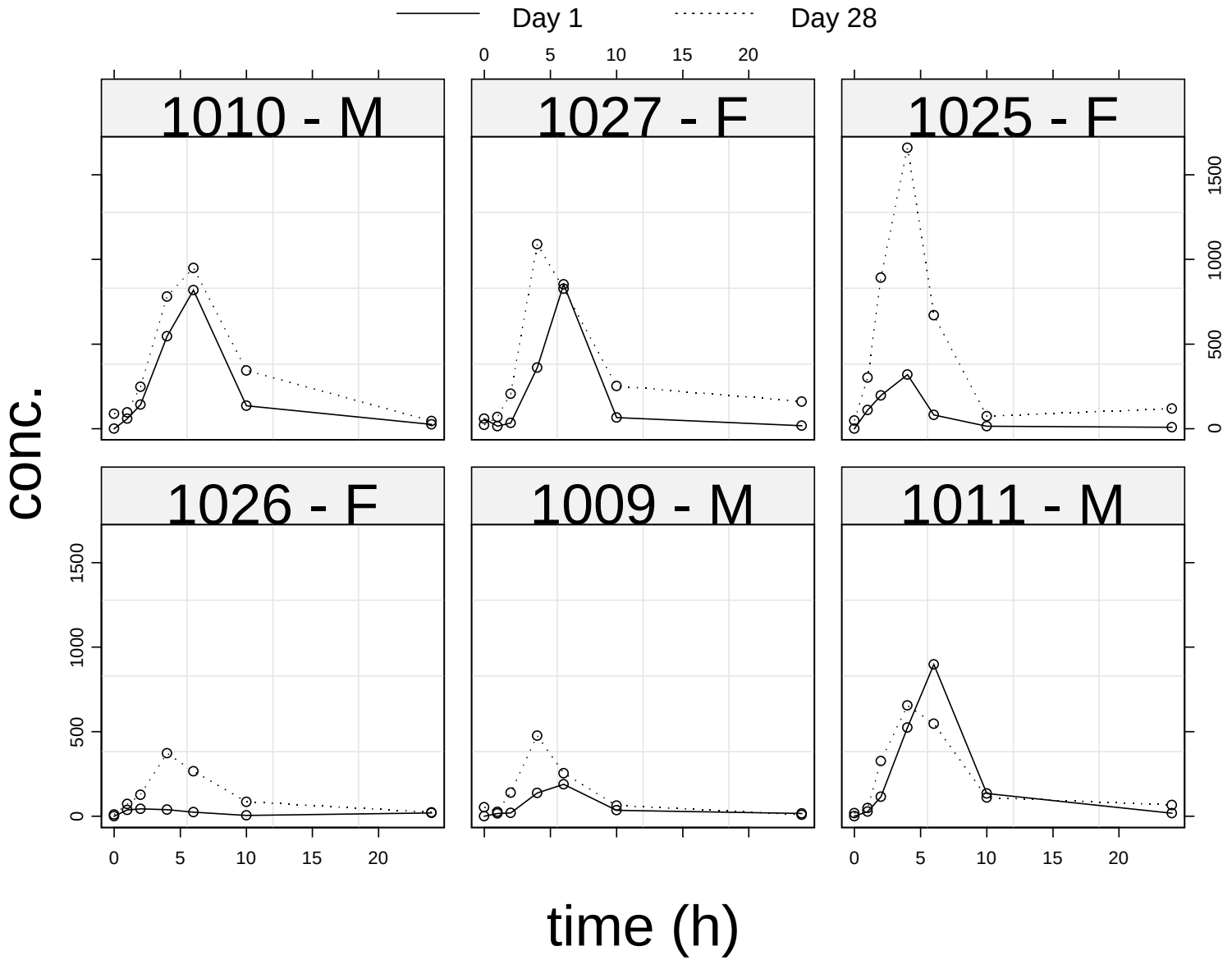
Plasma concentration-time profiles of NME-I in monkeys



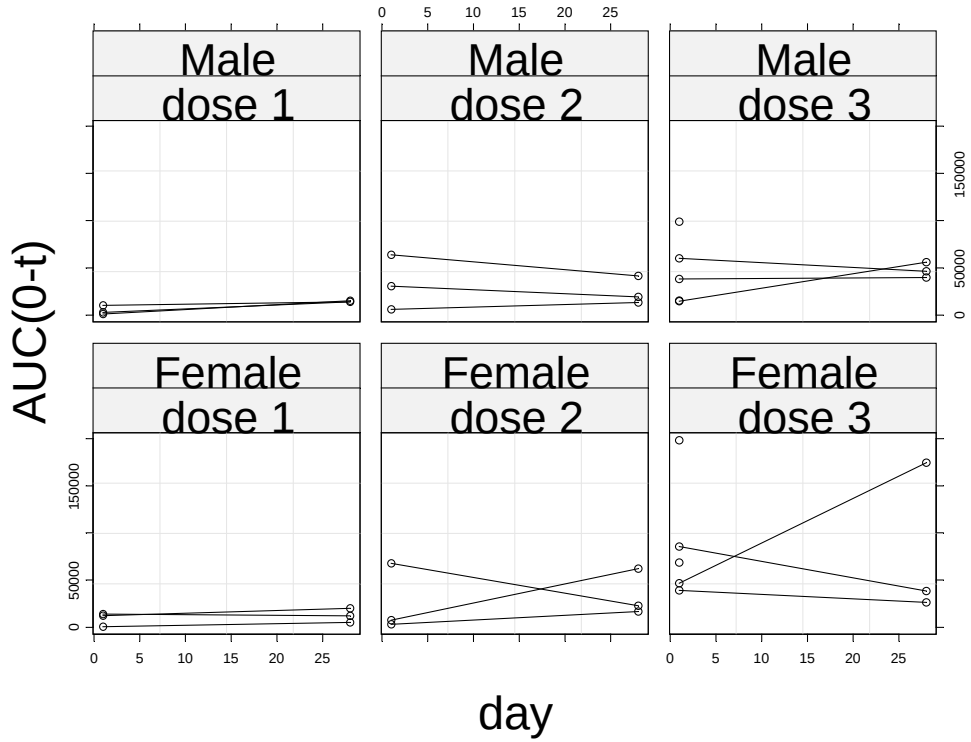
Plasma concentration-time profiles - NME-II in monkeys



Concentration-time profiles of NME-II in monkey - dose 2



NME-I exposure according to dose, day and gender
4-week toxicity study in monkey

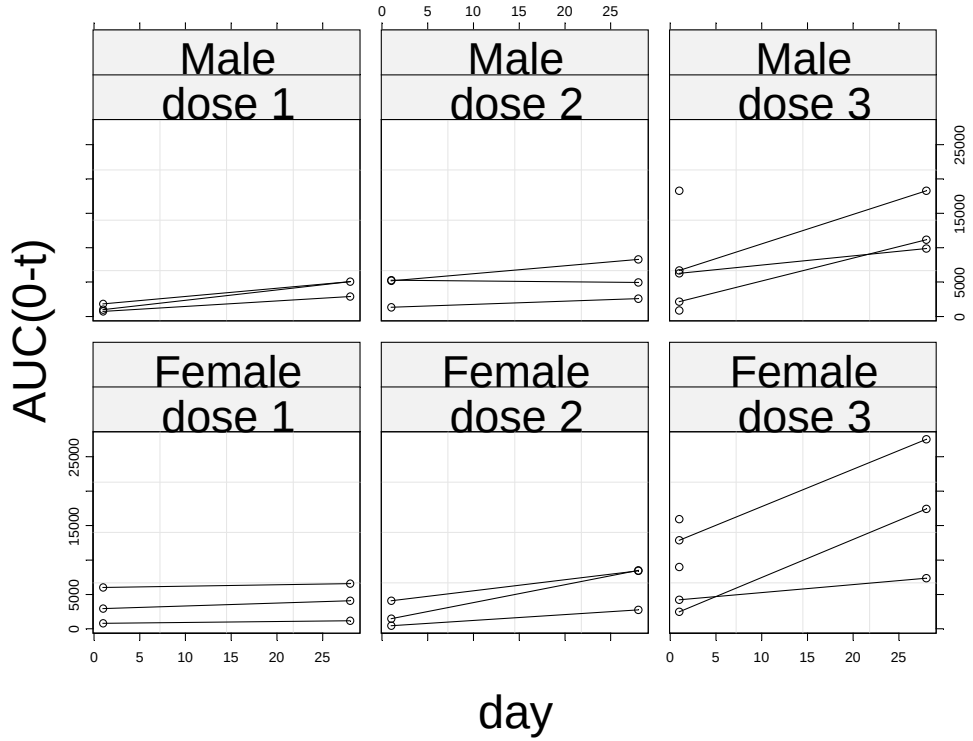


Linear mixed-effects model

```
Fixed effects: log(auctn) ~ dose + day + gender
                  Value Std.Error DF   t-value p-value
(Intercept)  8.910655 0.2125893 18  41.91489  <.0001
      dose1  0.191807 0.2178871 18   0.88030  0.3903
      dose2  0.173336 0.1134573 18   1.52776  0.1440
        day  0.019938 0.0098042 17   2.03361  0.0579
     gender -0.096715 0.1666107 18  -0.58048  0.5688
```

NME-I exposure time-, gender- and dose independent

NME-II exposure according to dose, day and gender
4-week toxicity study in monkey



Linear mixed-effects model

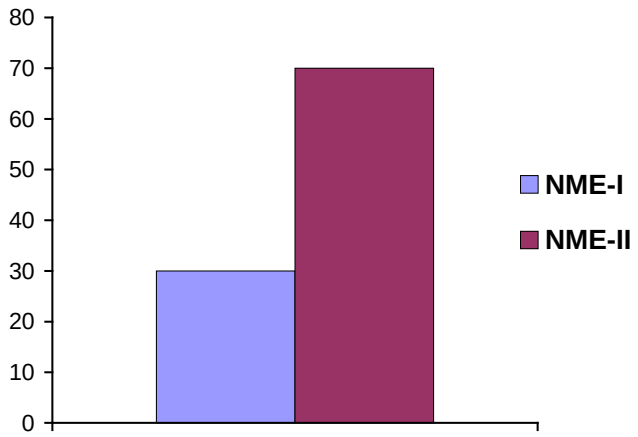
```
Fixed effects: log(auctn) ~ dose + day + gender
                  Value Std.Error DF   t-value p-value
(Intercept)  7.163447 0.1840747 18  38.91598  <.0001
      dose1 -0.186763 0.2214715 18  -0.84328  0.4101
      dose2  0.038003 0.1117525 18   0.34006  0.7377
        day  0.033537 0.0055627 17   6.02896  <.0001
     gender -0.093921 0.1658408 18  -0.56633  0.5782
```

NME-II exposure gender- and dose independent

NME-II exposure higher on day 28 than on day 1

Safety Pharmacology of combination
4-week toxicity study in monkey

Suspension
NME-I / NME-II ratio
30 / 70



Exposure
NME-I / NME-II ratios
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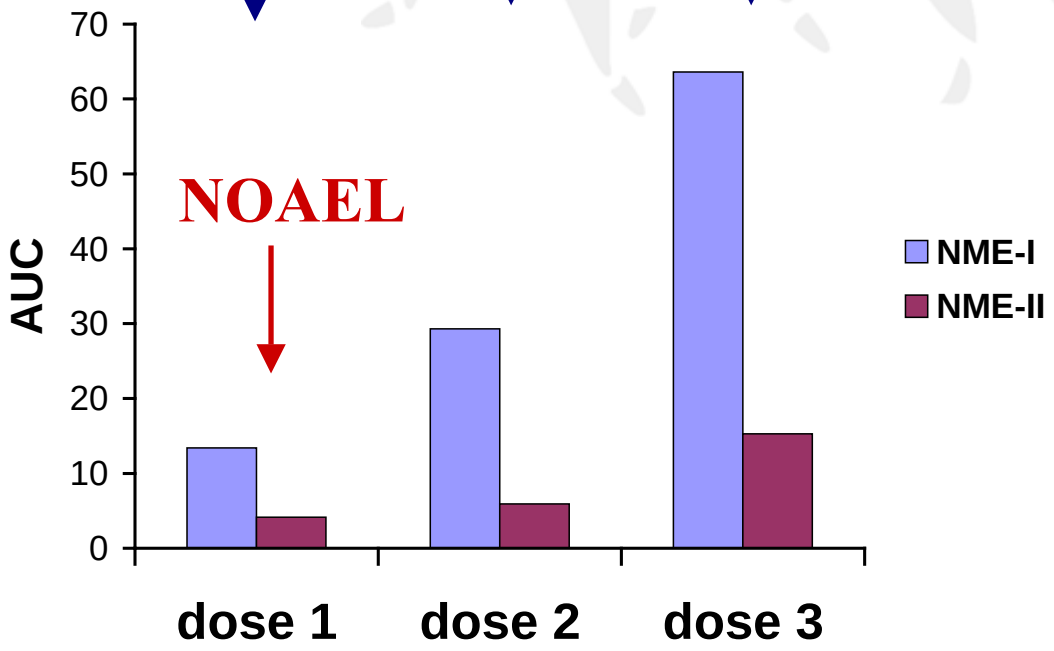

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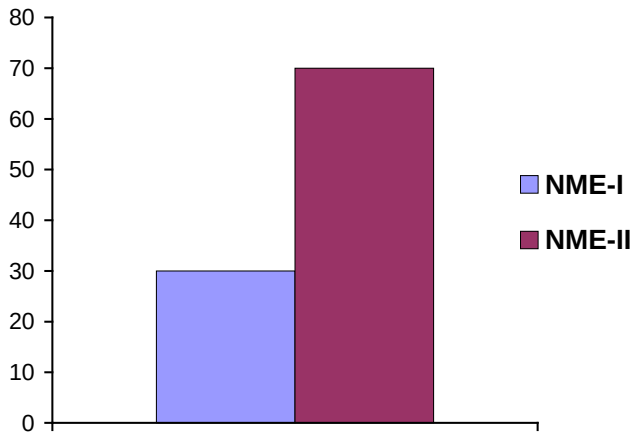
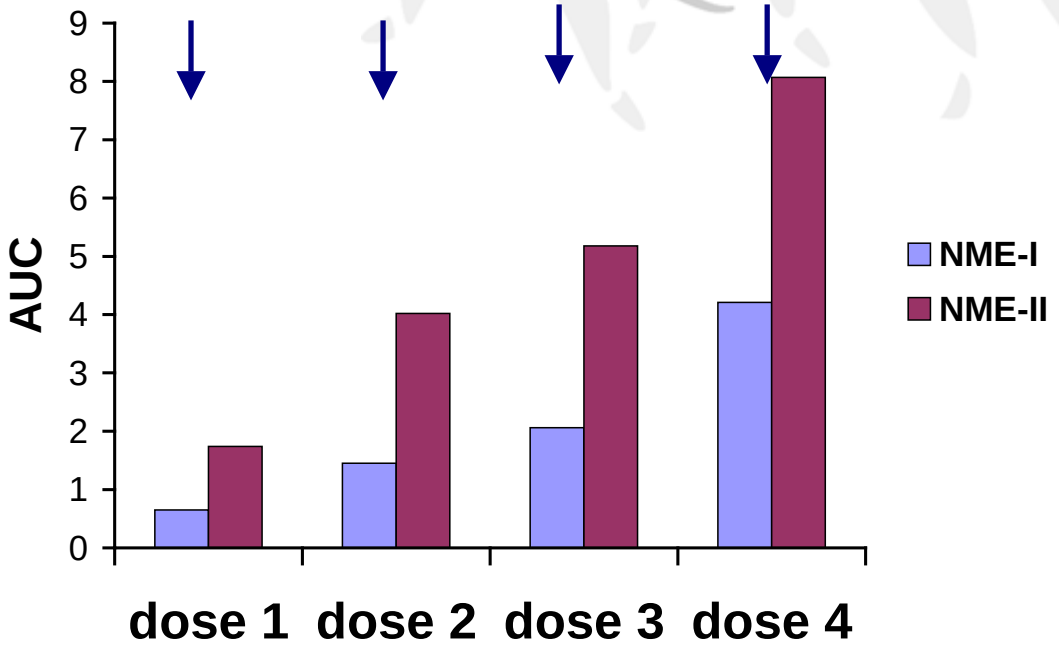
Safety Pharmacology of combination
First in man study

capsules
NME-I / NME-II ratio
30 / 70



Exposure
NME-I / NME-II ratios
27/73 27/73 28/72 34/66



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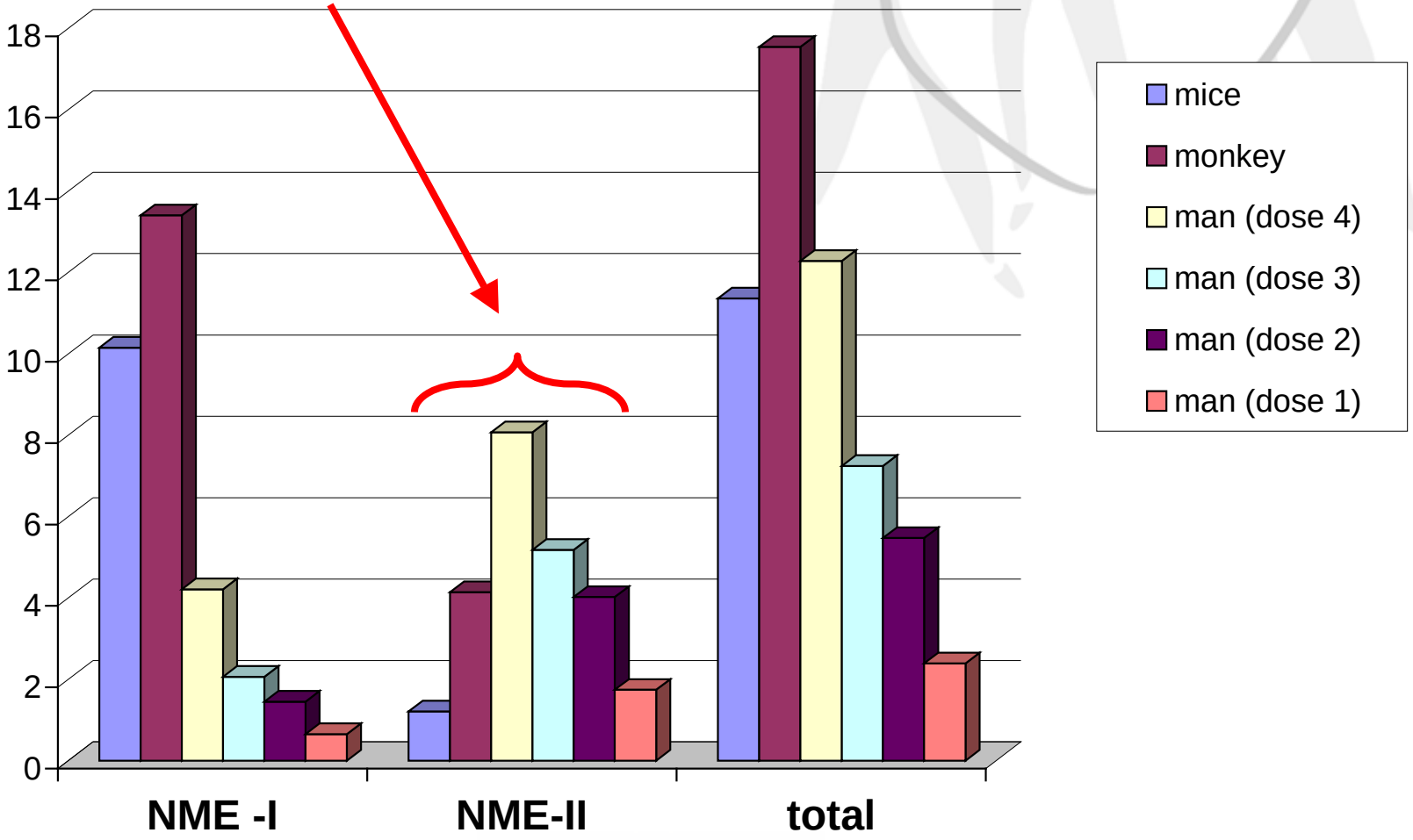
Plasma exposures in man vs. mouse and monkey at NOAEL

NME-II exposures in Humans > than those at NOAEL in mice and monkeys



What are the Consequences for the Multiple-Dose Study in Healthy Volunteers?

Recommendation is not to exceed the exposures achieved at NOAEL in monkeys (for NME-1 as well as NME-II):

→ Top dose in the MD study should be limited to **dose 1 or 2**, to account for the exposure in NME-II achieved in HV

→ Need to assess higher doses in the MD study as the active dose is estimated close to dose 2

⇒ Need for additional tox studies to allow higher doses in the MD study

Action Plan to Support Multiple-Dose at Doses > dose 2 in Healthy Volunteers

Perform studies in monkeys using individual components with the aims of:

- Determine the relationship between toxicity and exposures to NME-I and to NME-II: toxicity related to NME-I, to NME-II or to NME-I + NME-II ?
- Determine, if possible, a safety margin for NME-II (limiting factor to increase doses in man)

Tox Proposal to Support Multiple-Dose at Doses > dose 2 in Healthy Volunteers

Proposed Studies in monkeys:

- Rising dose study with clinical obs. and TK → determination of the MTD and the exposure achieved for NME-I and for NME-II:
  - sufficient exposure obtained ?

Yes →

- 5-day exploratory study with determination of the MTD and the exposure achieved for NME-I and for NME-II
- 4-week toxicity study with TK and determination of safety margin

No →

Need Pharm. Sciences support to define the formulation to be used (oral, IV ?)

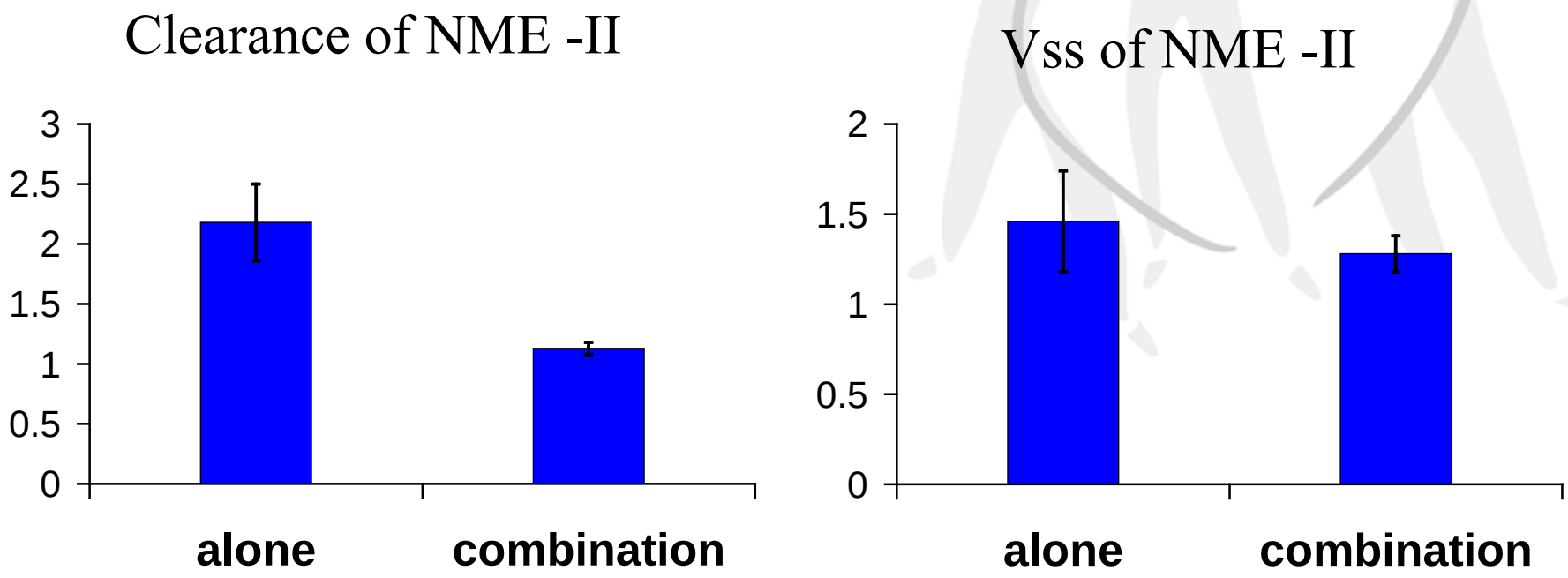
Tox Proposal to Support Multiple-Dose at Doses > dose 2 in Healthy Volunteers

Proposed Study Plan for the 4-week study in monkeys:

- 6 to 8 groups:
  - ✓ 1 control group
  - ✓ 1 “positive group” i.e. treated with the 30/70 combination
  - ✓ 2 or 3 groups treated with NME-I
  - ✓ 2 or 3 groups treated with NME-II

- Standard examinations (for regulatory purposes)

PK interaction between NME-1 and NME-2
CL and Vss of NME-II in monkeys (single dose / IV route)



- NME-I is CYP3A4 inhibitor. NME-I decreases plasma clearance of co-administered NME-II by a factor of about 2

Conclusion

- Because the dose ratio may change during drug development, it is important to design the toxicity studies to provide adequate margins of safety for future clinical trials
- PK/ADME studies are recommended to assess the potential for a PK interaction between the drugs (in vitro drug metabolism studies be conducted early in drug development)