Pharmacodynamics of F901318 against *Aspergillus fumigatus* in a rabbit model of invasive pulmonary aspergillosis

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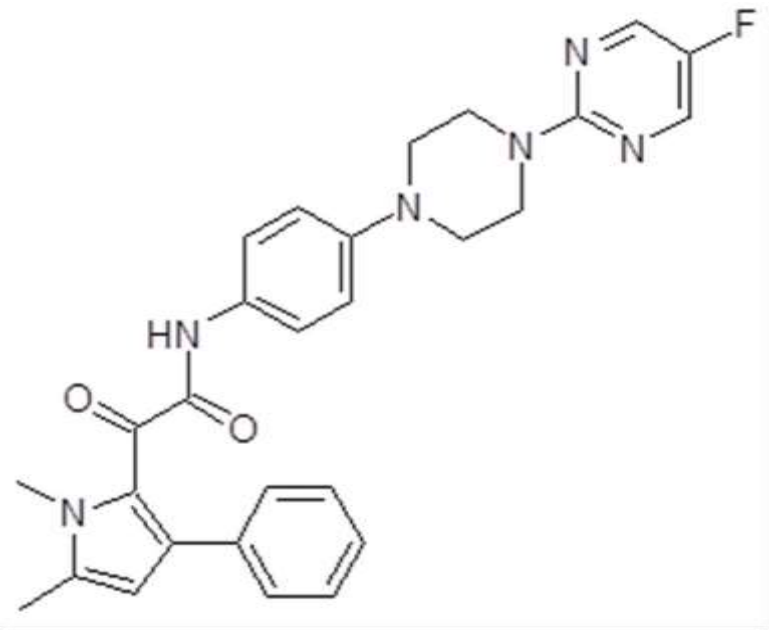
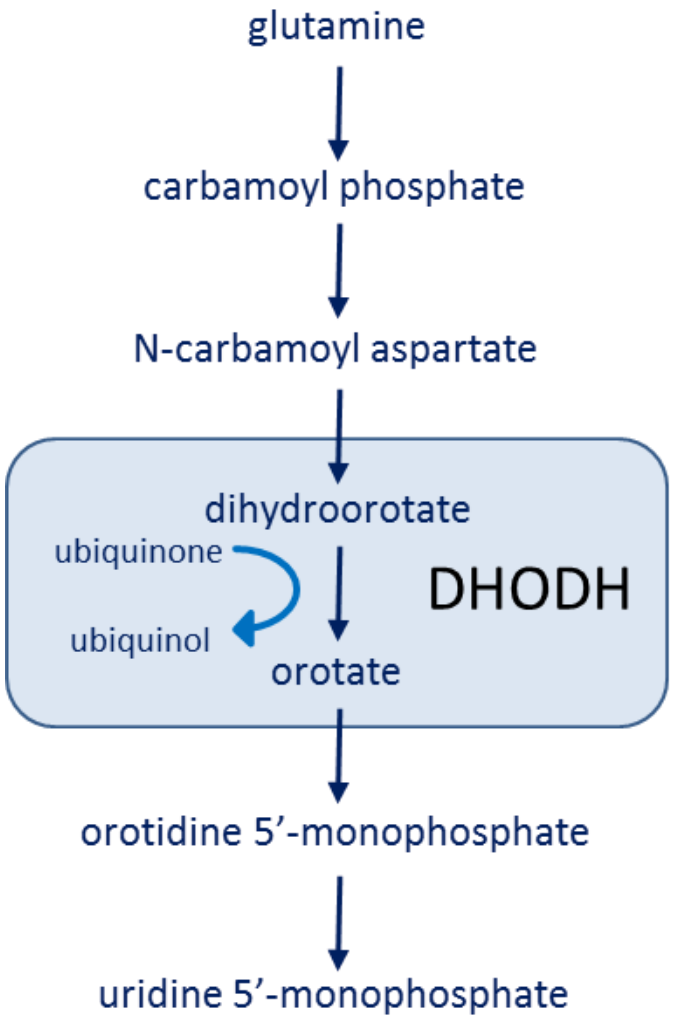
Background

- Invasive aspergillosis is a relatively common infection with mortality of 20-30%
- Triazole resistance in *Aspergillus fumigatus* is increasingly reported
  - Mortality is 88-100%
  - Treatment options poorly defined
- All antifungal agents have relative high rates of adverse events

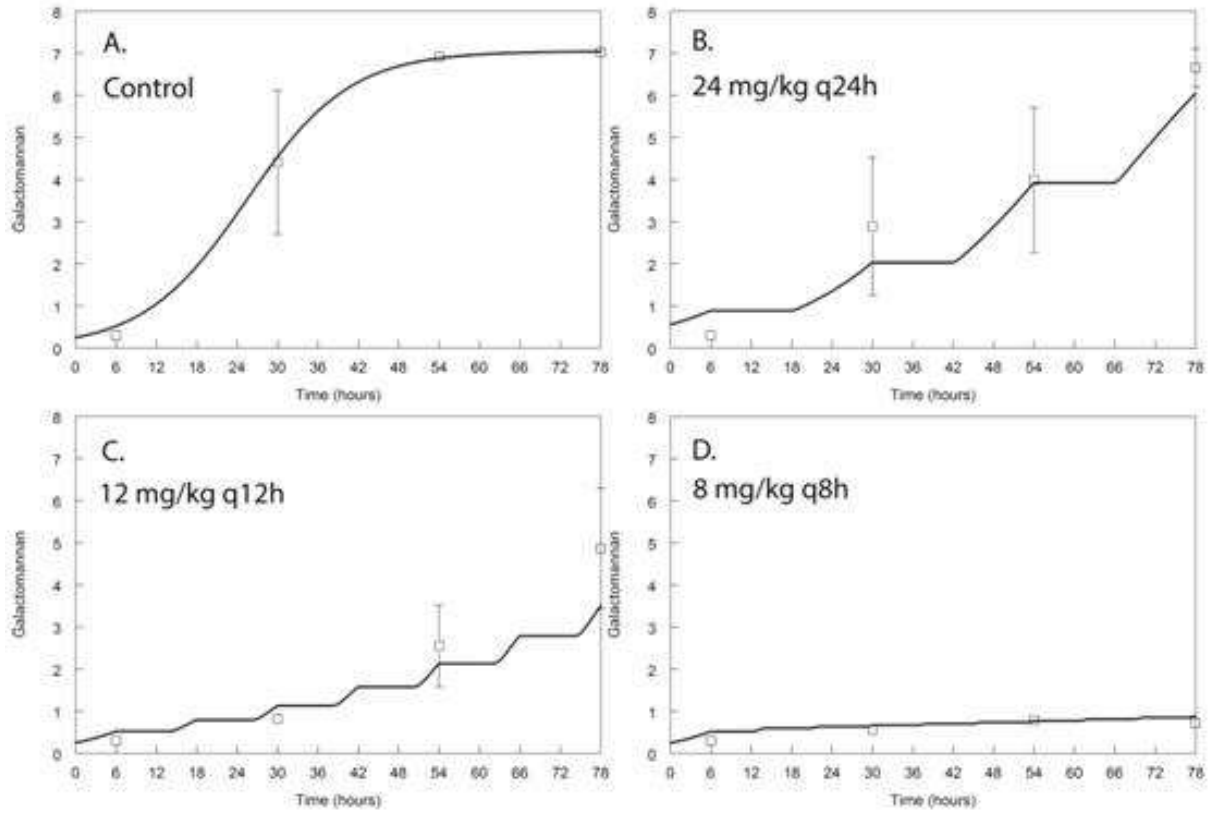
F901318 is a new agent with a novel mechanism of action[1]





[1]Oliver et al PNAS 113(45) 2016

Preclinical PK-PD of F901318
Threshold (or time) dependent antifungal activity: Cmin or Cmin:MIC is the relevant dynamically linked variable



Hope et al 55th ICAAC San Diego

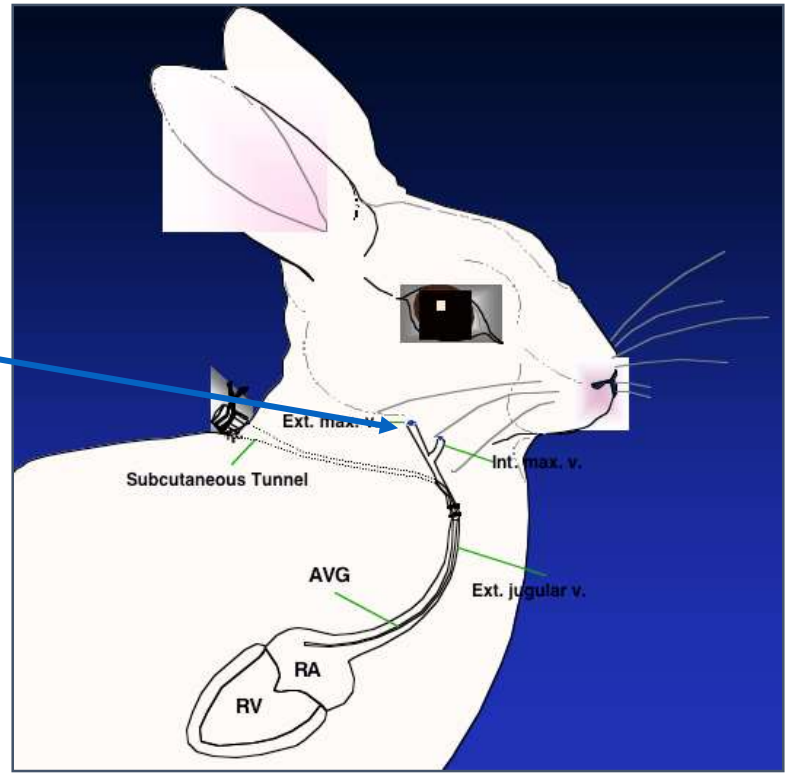
Aims of Current Study

1. Define the pharmacokinetics-pharmacodynamics (PK-PD) of F901318 against *Aspergillus fumigatus* NIH/4215 (MIC 0.03 mg/L) in a well characterised rabbit model of IPA
2. Identify the magnitude of the relevant pharmacodynamic index linked with a favorable outcome in rabbits and mice

Rabbit model of invasive pulmonary aspergillosis-1

- Male New Zealand White rabbits

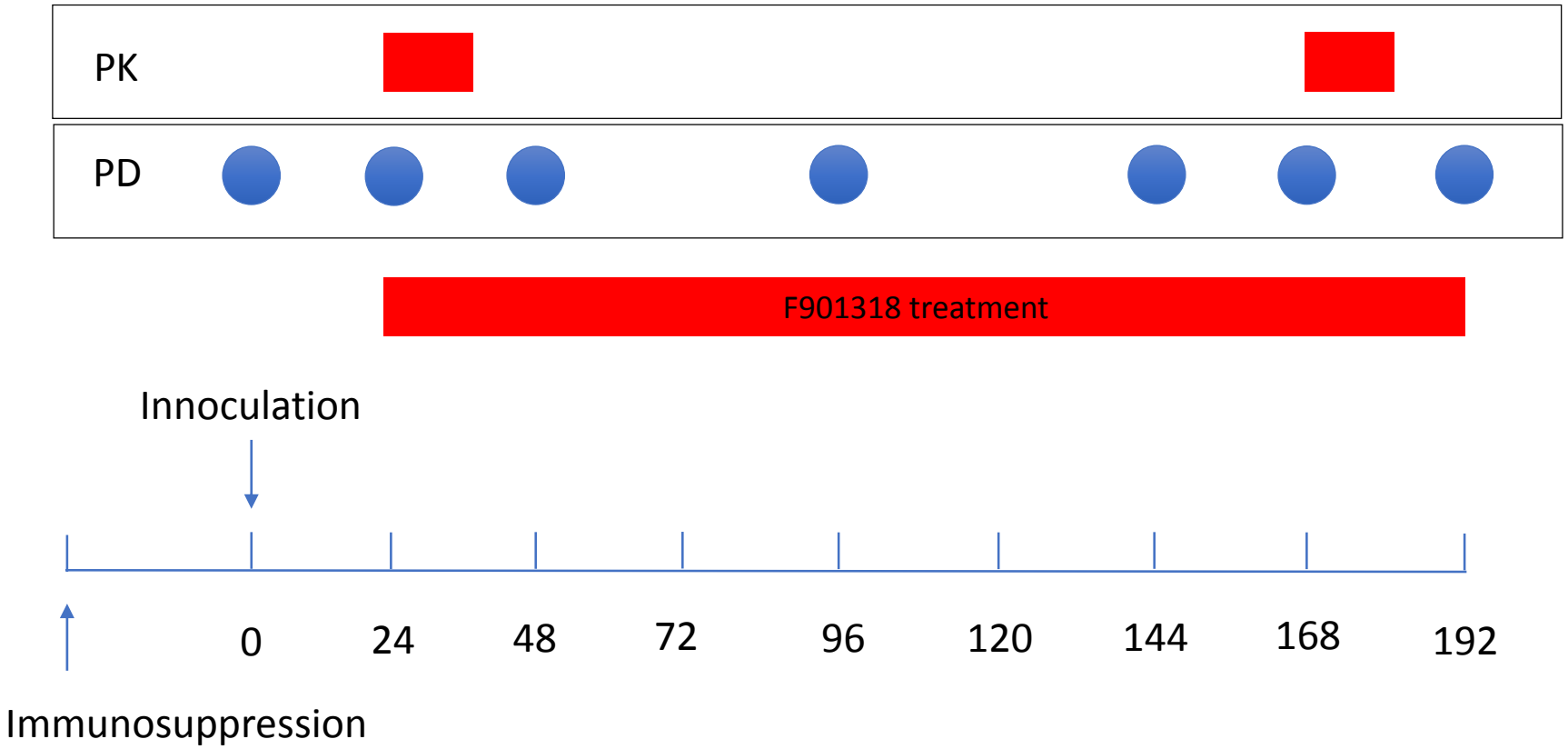
- Central silastic venous catheter permits repeated atraumatic venous access



Rabbit model of invasive pulmonary aspergillosis-2

- Neutropenia induced with
  - Cytosine arabinoside 525 m^2 day -1
  - Methylprednisolone 5 mg/kg day -1
- Opportunistic bacterial infection prevented
  - Vancomycin 15 mg/kg/day
  - Gentamicin 5 mg/kg alternate days
  - Ceftazidime 75 mg/kg q12h

Experimental Design



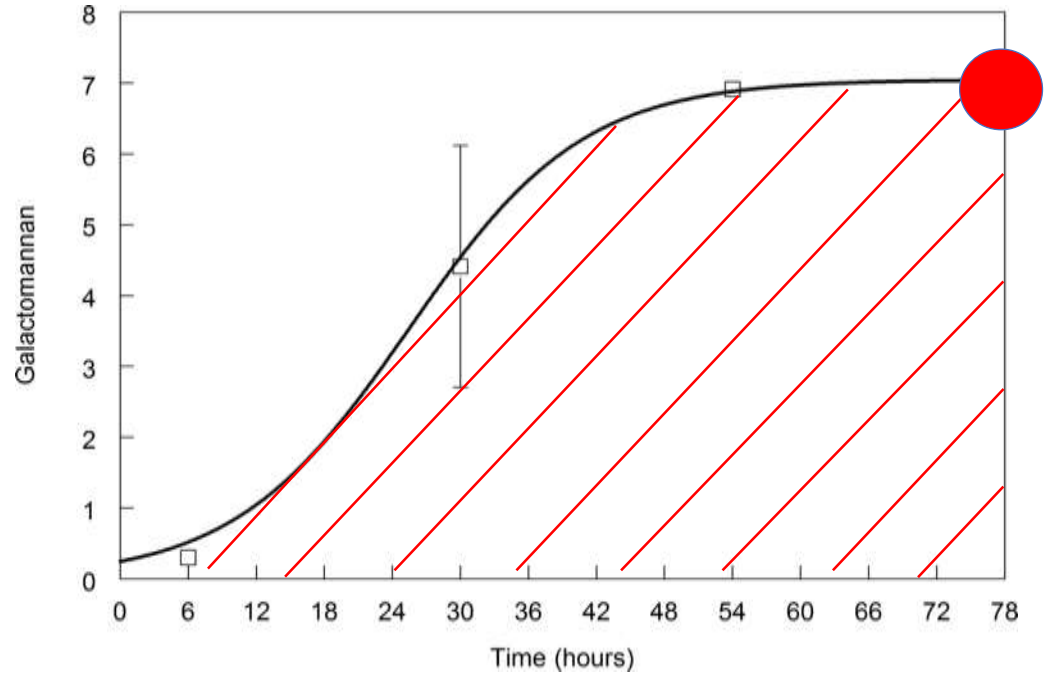
F901318 Regimens & Study Endpoints

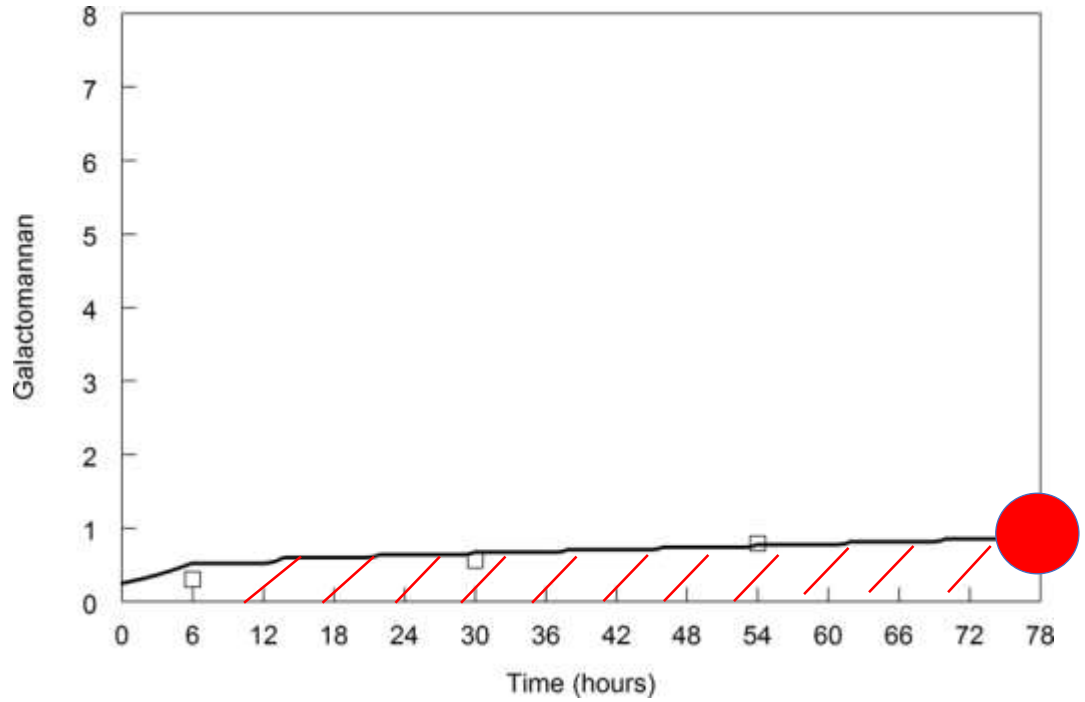
- F901318
  - Chosen on basis of preliminary tolerability studies with embedded PK
  - Vehicle control, 0.5, 2.5, 5, 10 mg/kg q12h orally
- F901318 plasma concentrations measured by HPLC
- Galactomannan measured by BioRad double sandwich ELISA according the the manufacturer's instructions
- Cmin, GM at t=78 hr., and area under GM-time curve t=0 to t=78 hr. used as study endpoints

$$XP(1) = B(1) - Ka * X(1)$$

$$XP(2) = Ka * X(1) - \left(\frac{SCL}{V}\right) * X(2) - Kcp \cdot X(2) + Kpc \cdot X(3)$$

$$XP(3) = Kcp \cdot X(2) - Kpc \cdot X(3)$$


Galactomannan
Time (hours)
0
1
2
3
4
5
6
7
8
0
6
12
18
24
30
36
42
48
54
60
66
72
78


Galactomannan
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0
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2
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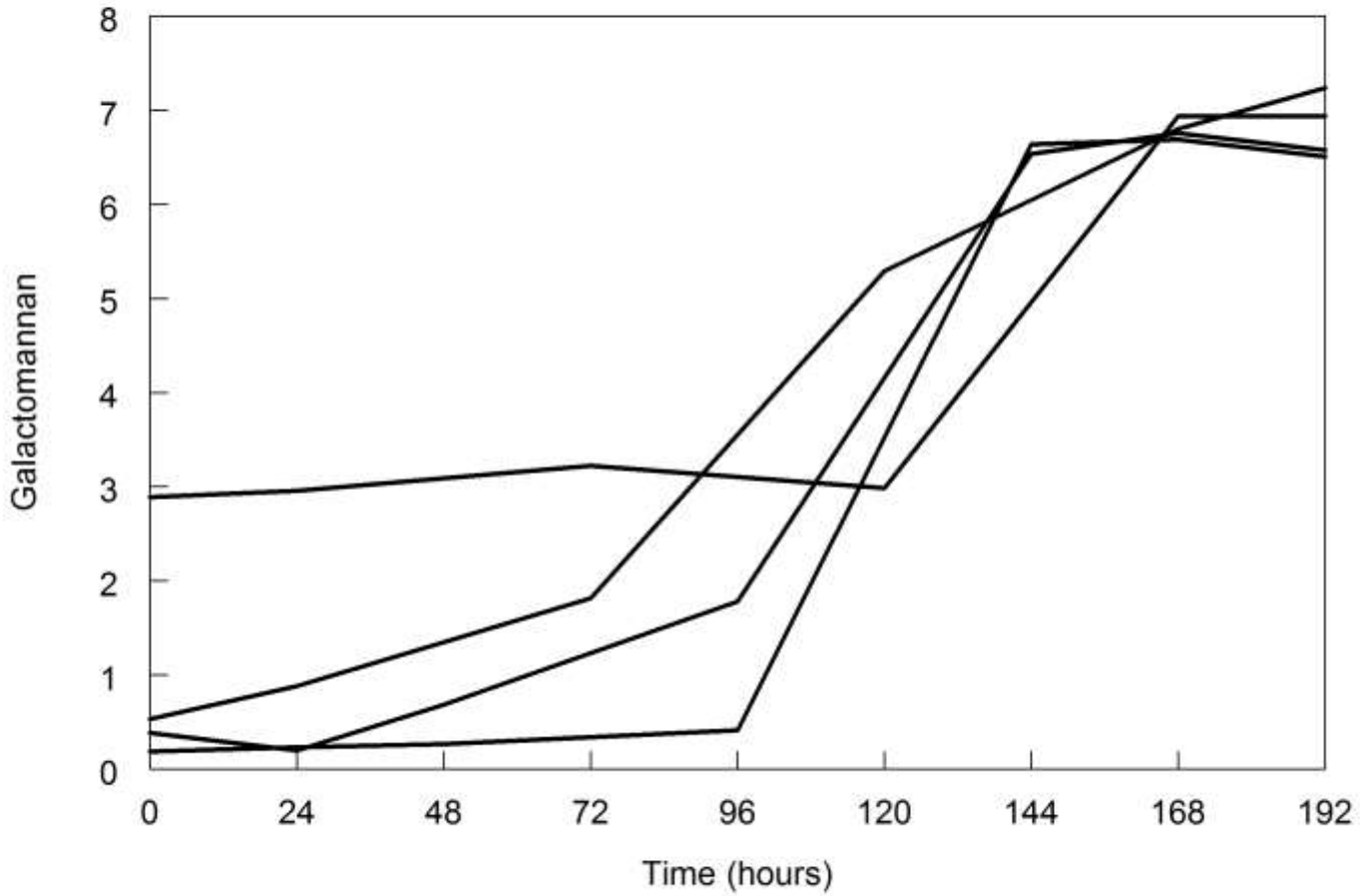
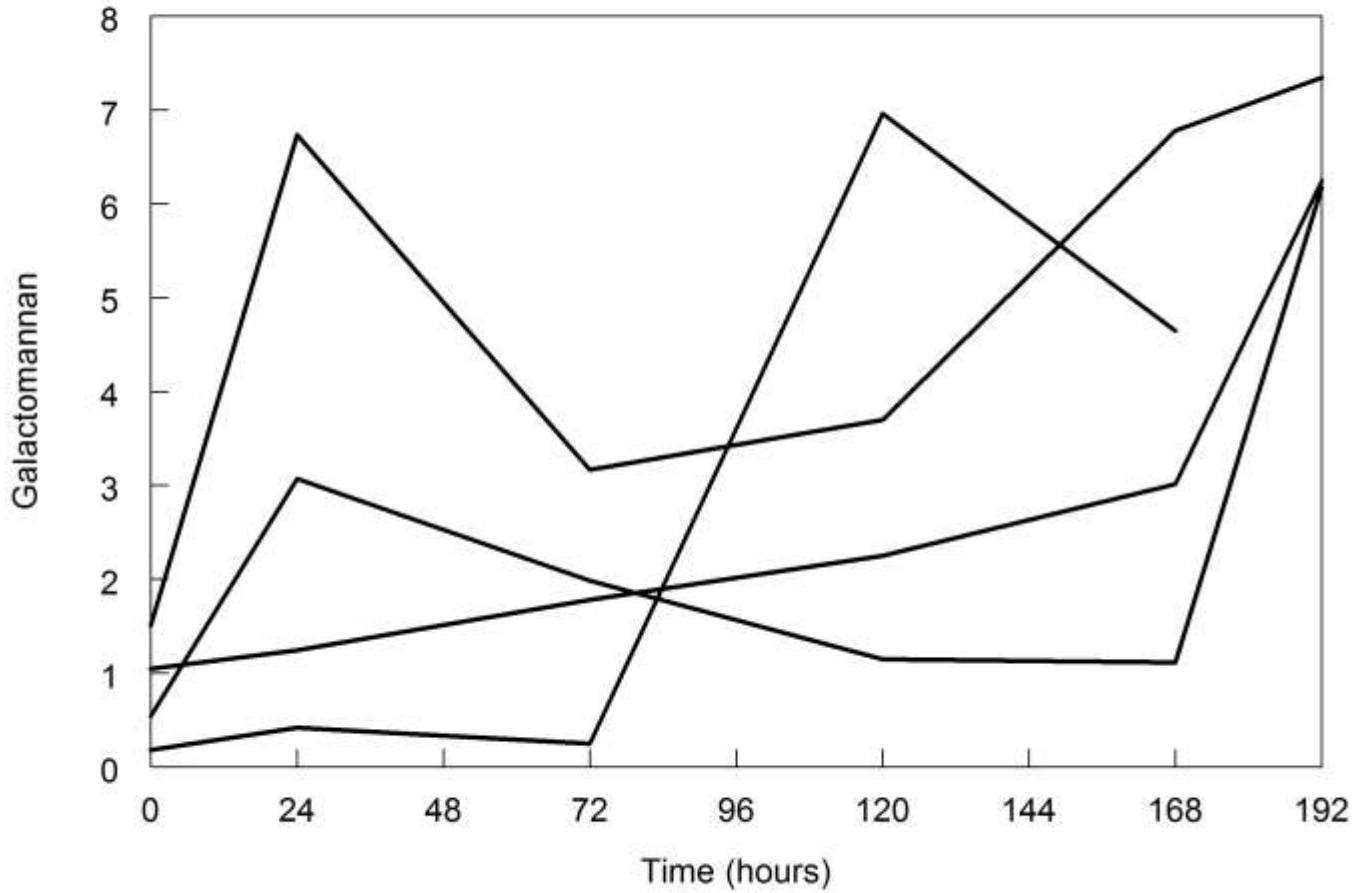
78

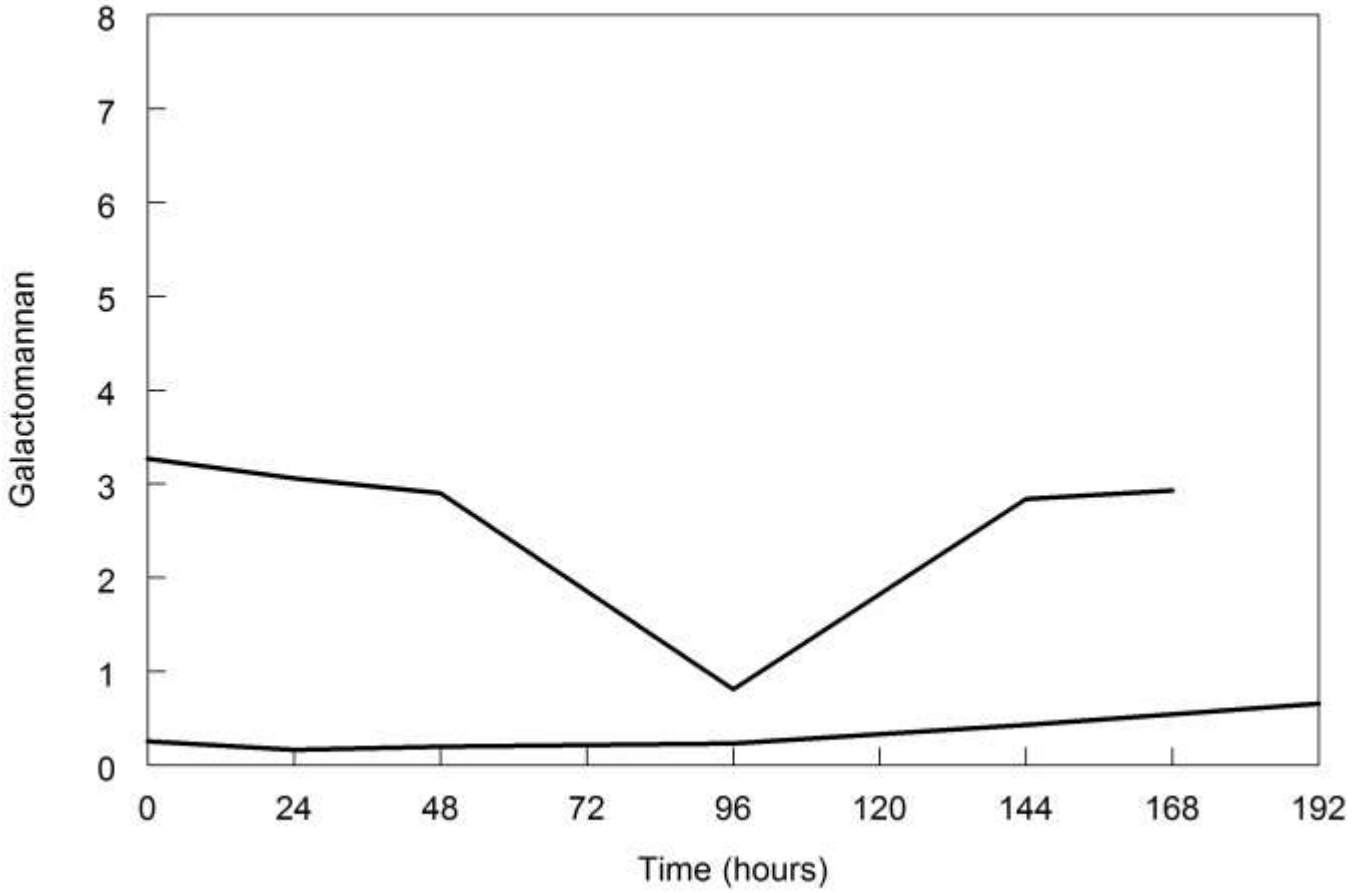
Results-Controls



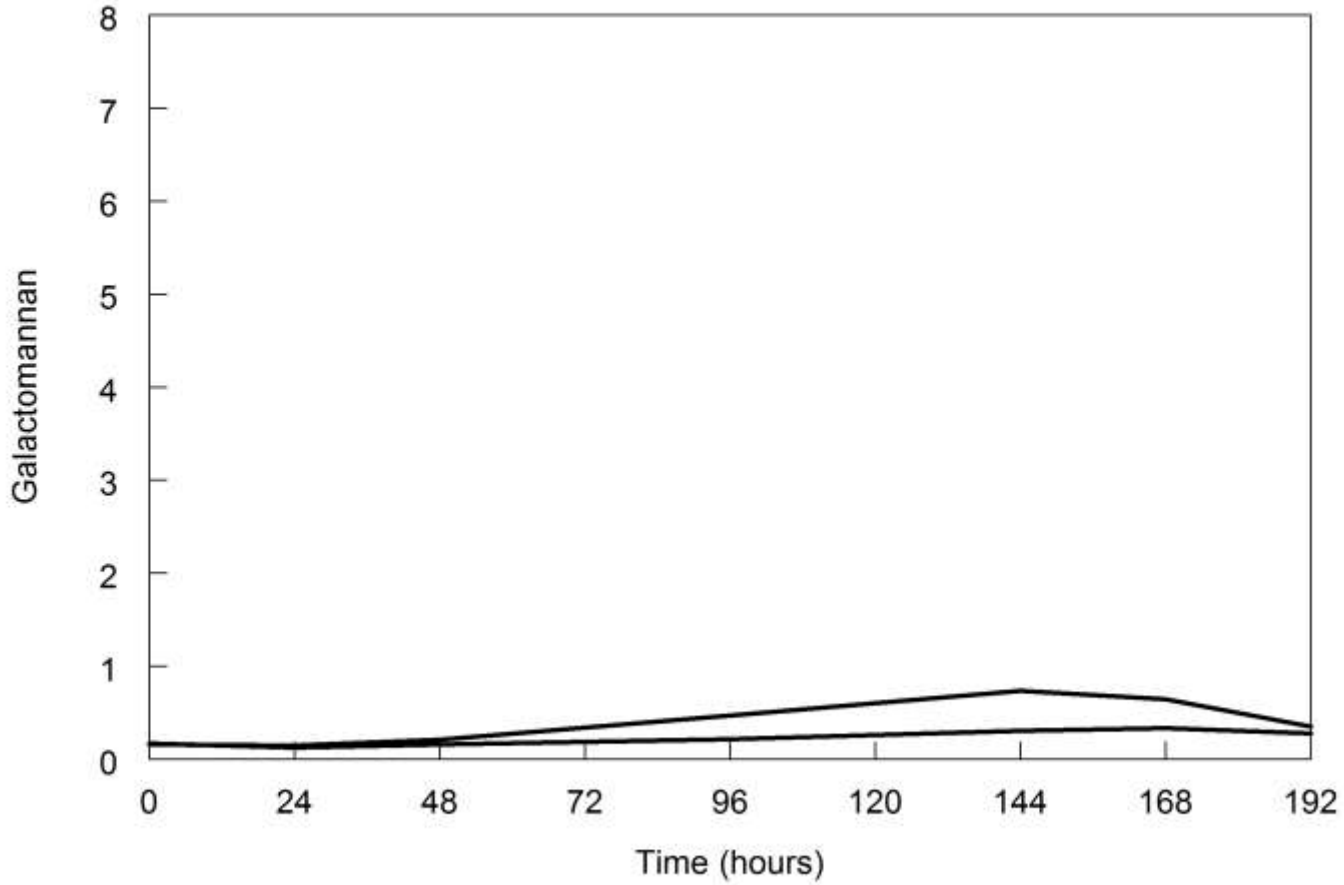
F901318 0.5 mg/kg q12h orally



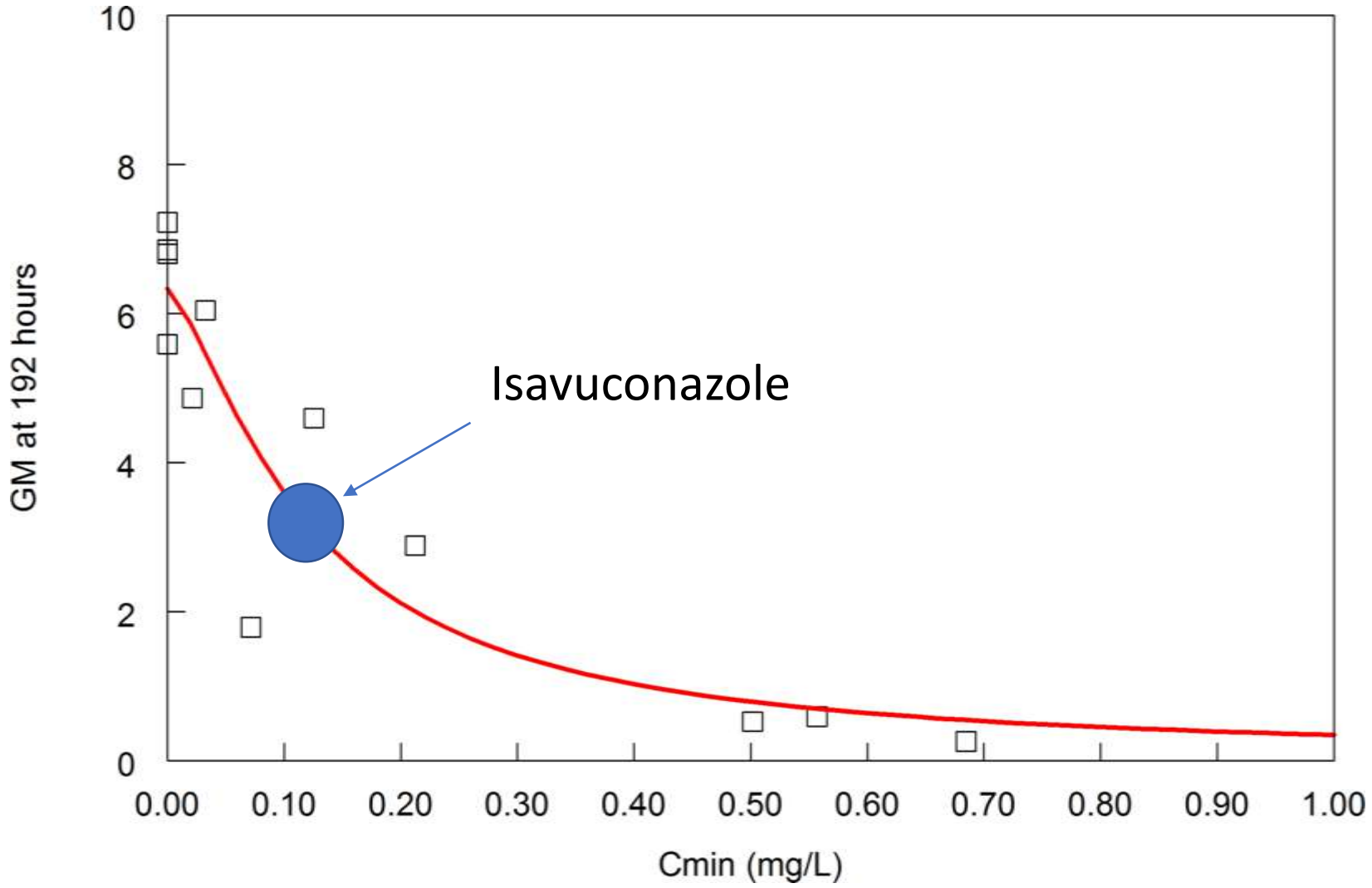
F901318 5 mg/kg q12h orally



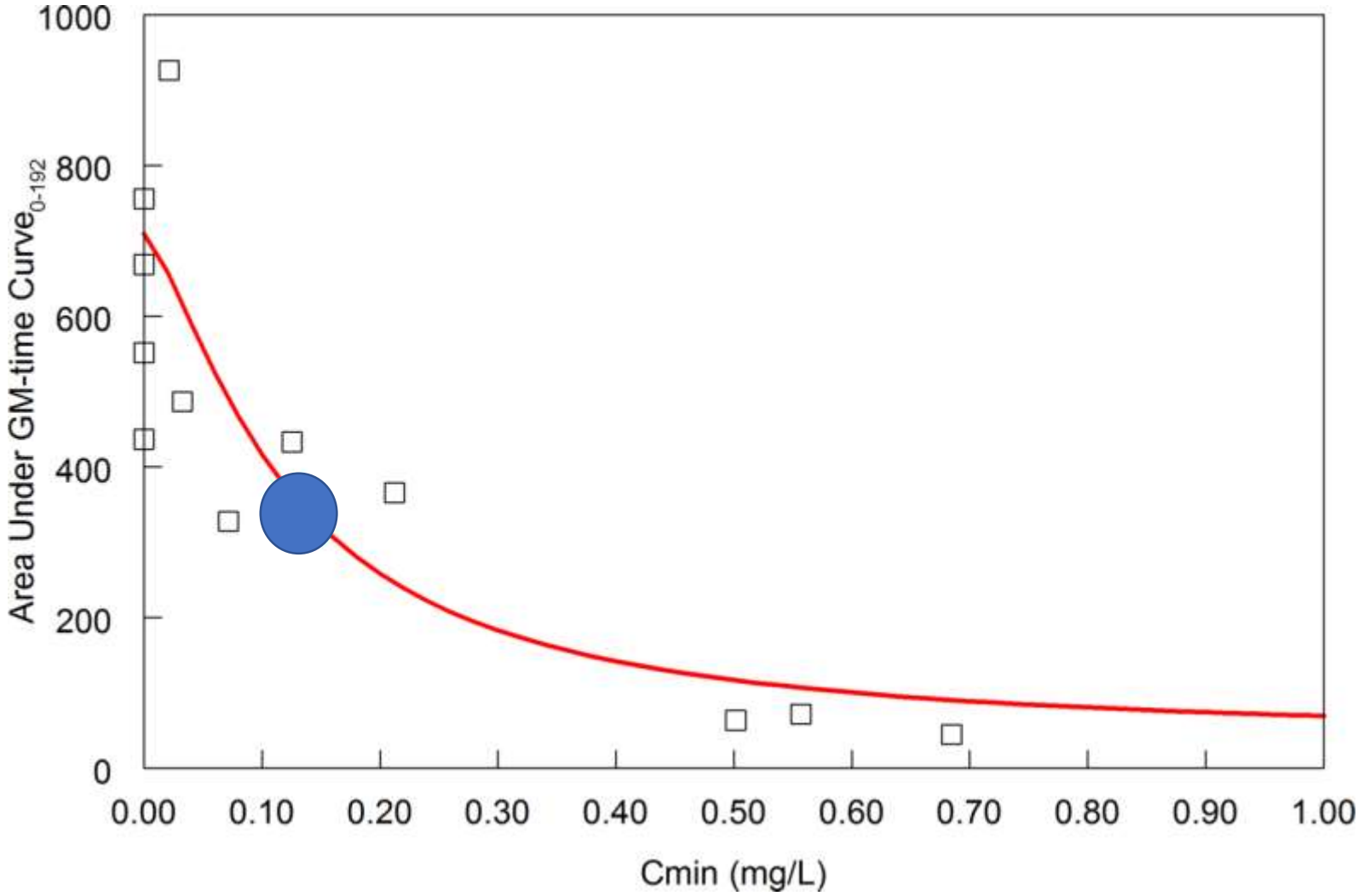
F901318 10 mg/kg q12h orally



GM at the end of the experiment vs. Cmin



Area under GM-time curve vs. Cmin



Conclusions

- F901318 induces a dose (and exposure) dependent decline in galactomannan in a severely neutropenic rabbit model
- Licensed regimen of isavuconazole in this model induces half-maximal reduction in GM
- Regimens of F901318 for Phase II & III must match or exceed isavuconazole
  - i.e. Cmin > 0.1-0.2 mg/L