# FIGURES

**Fig. 1a:**

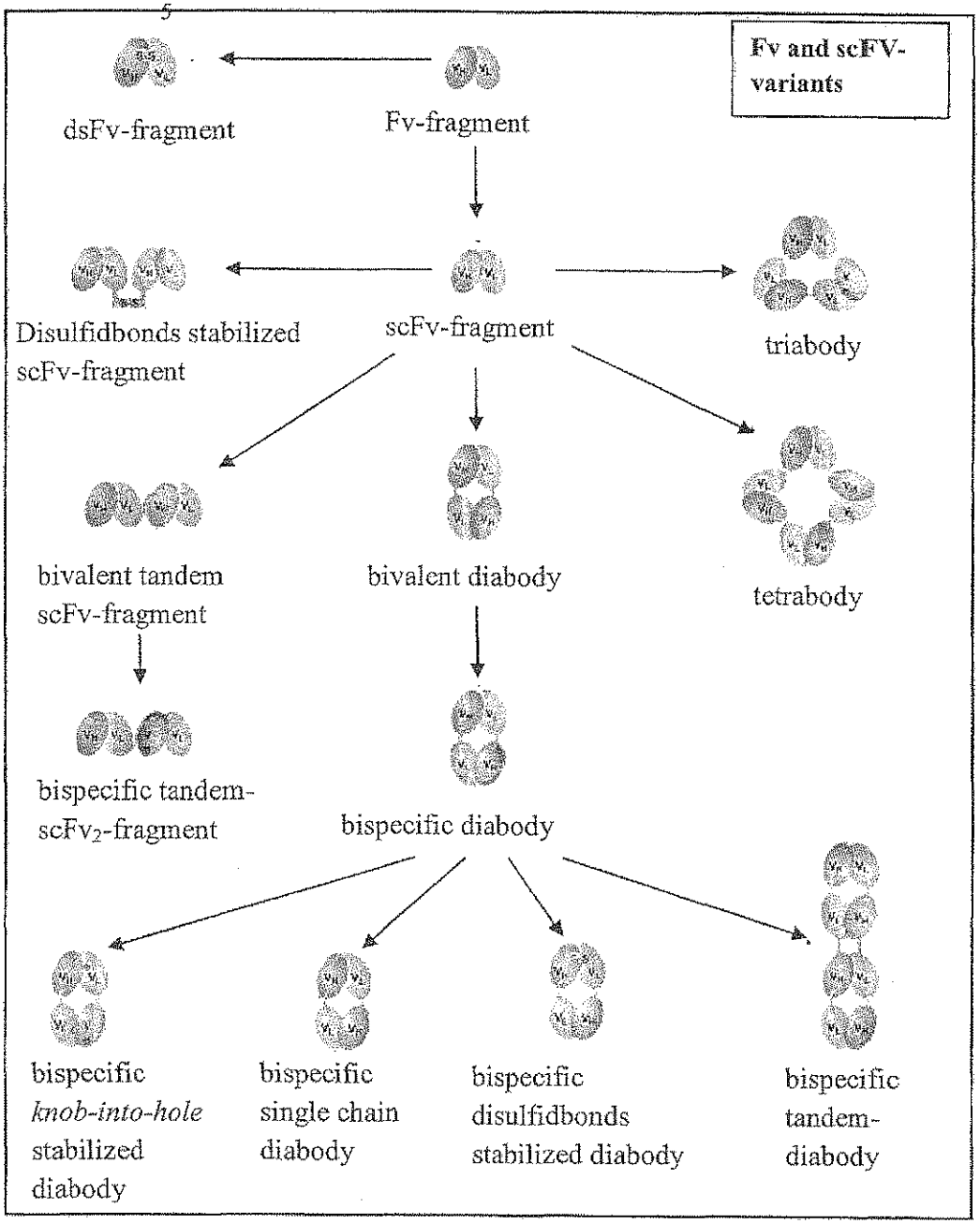


Fig 1b:

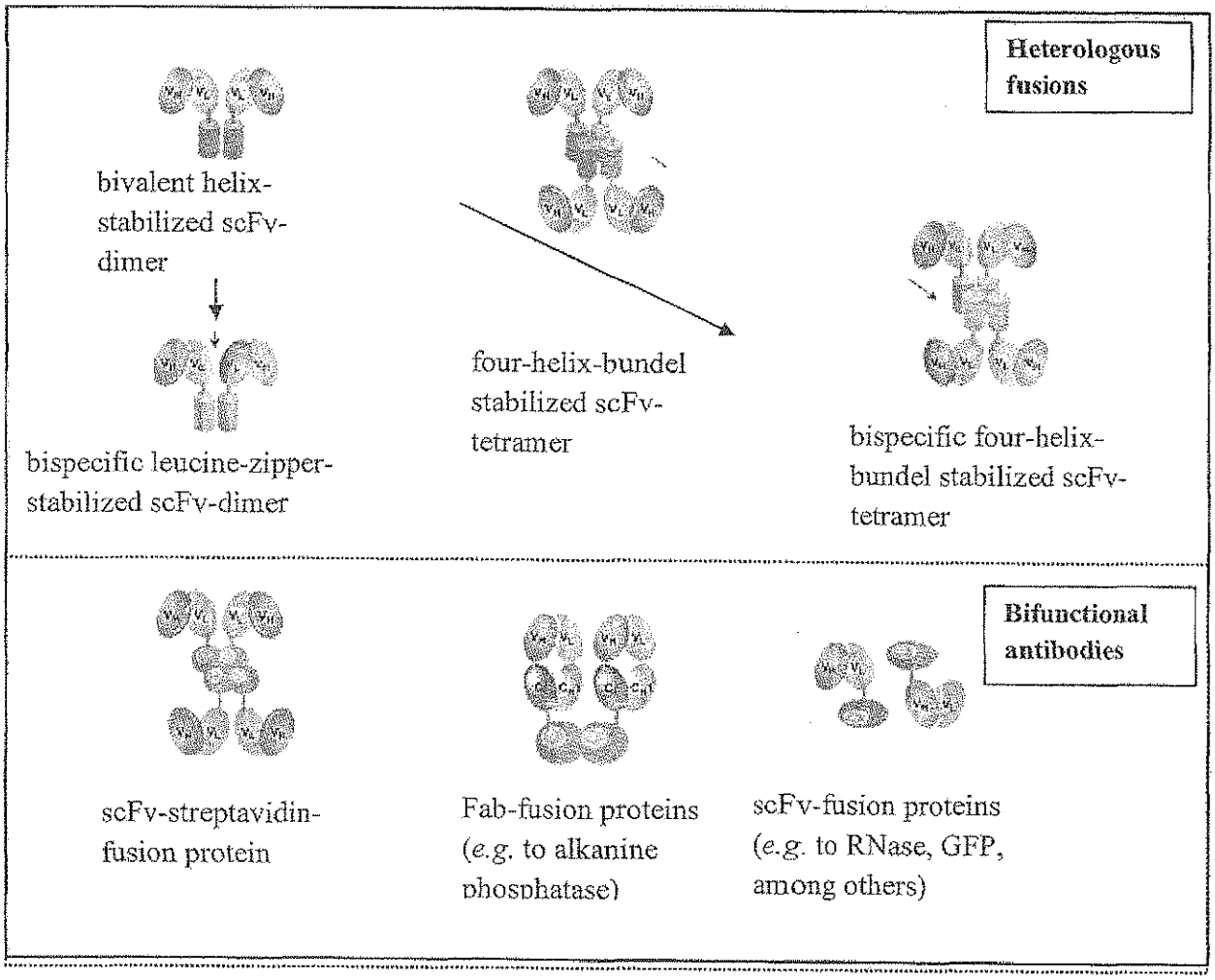

Heterologous fusions
bivalent helix-stabilized scFv-dimer
bispecific leucine-zipper-stabilized scFv-dimer
four-helix-bundel stabilized scFv-tetramer
bispecific four-helix-bundel stabilized scFv-tetramer
Bifunctional antibodies
scFv-streptavidin-fusion protein
Fab-fusion proteins (e.g. to alkanine phosphatase)
scFv-fusion proteins (e.g. to RNase, GFP, among others)

**Fig. 1c:**

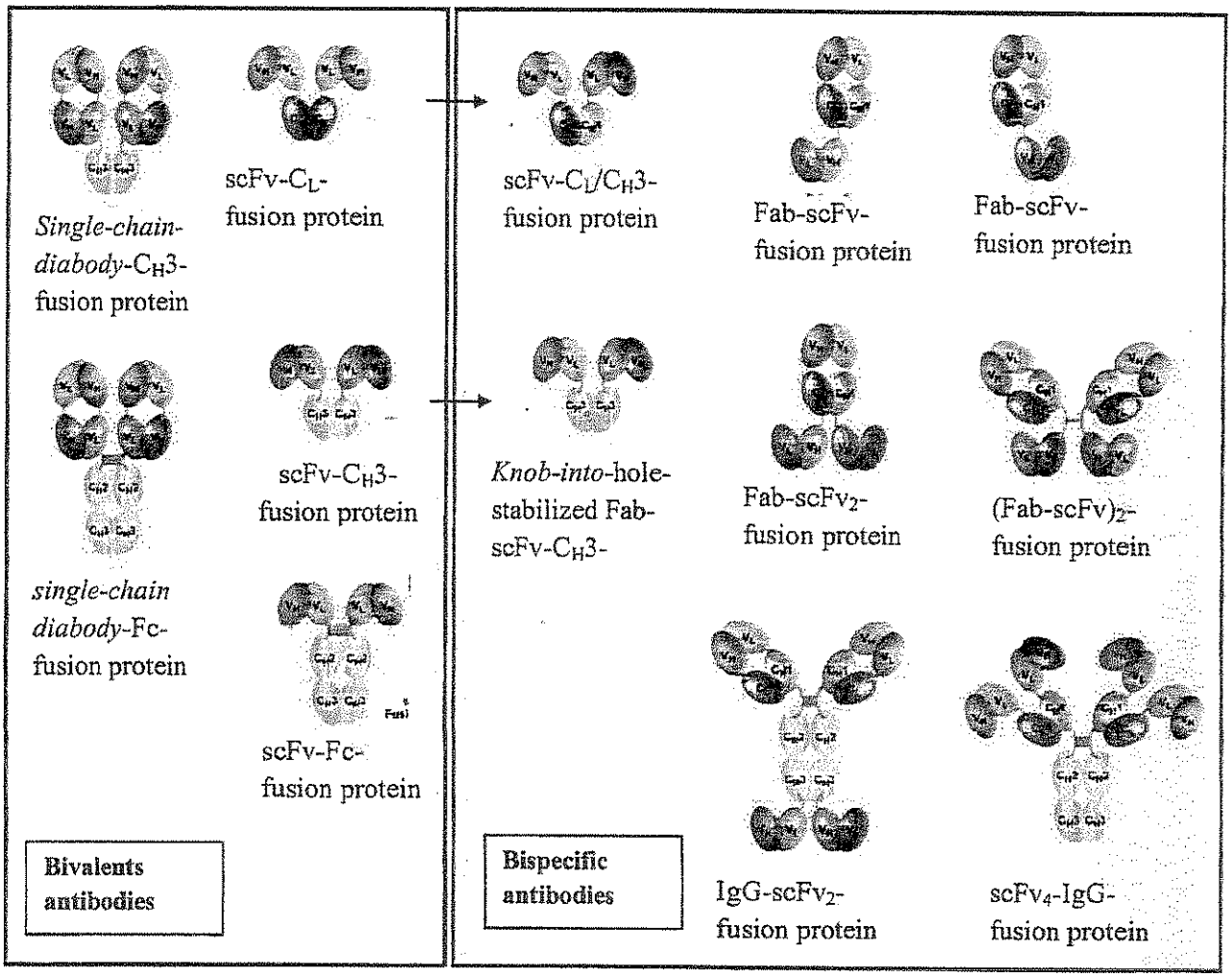

*Single-chain-diabody*-$C_H3$-fusion protein
scFv-$C_L$-fusion protein
scFv-$C_L$/$C_H3$-fusion protein
Fab-scFv-fusion protein
Fab-scFv-fusion protein
*single-chain diabody*-Fc-fusion protein
scFv-$C_H3$-fusion protein
*Knob-into*-hole-stabilized Fab-scFv-$C_H3$-
Fab-scFv$_2$-fusion protein
(Fab-scFv)$_2$-fusion protein
scFv-Fc-fusion protein
IgG-scFv$_2$-fusion protein
scFv$_4$-IgG-fusion protein
**Bivalents antibodies**
**Bispecific antibodies**

**Fig. 2:**

SEQ ID NO: 21

**YRQSMNNFQGLRSFGCRFGTCTVQKLAHQIYQFTDKDKDNVAPRSKISPQGY-$NH_2$**

SEQ ID NO: 22

**YRQSMNQGSRSNGCRFGTCTFQKLAHQIYQLTDKDKDGMAPRNKISPQGY-$NH_2$**

SEQ ID NO: 23

**YRQSMNNFQGLRSFGCRFGTC**

SEQ ID NO: 24

**YRQSMNNFQGLRSFGCRFGTCTVQKLAHQIYQFTDKDKDNVA**

SEQ ID NO: 25

**PRSKISPQGY-NH2**

SEQ ID NO: 26

**YRQSMNNFQGLRSF**

SEQ ID NO: 27

**YRQSMNNFQG**

SEQ ID NO: 28

**YRQSMN**

SEQ ID NO: 29

**YRQSMNNFQGLRSFGCRFGTCTVQKLAHQIYQ**

SEQ ID NO: 30

**YRQSMNQGSRSNGCRFGTCTFQKLAHQIYQLTDKDKDGMA**

SEQ ID NO: 31

**YRQSMNQGSRSNGCRFGTCTFQKLAHQIYQL**

Fig. 3 a:

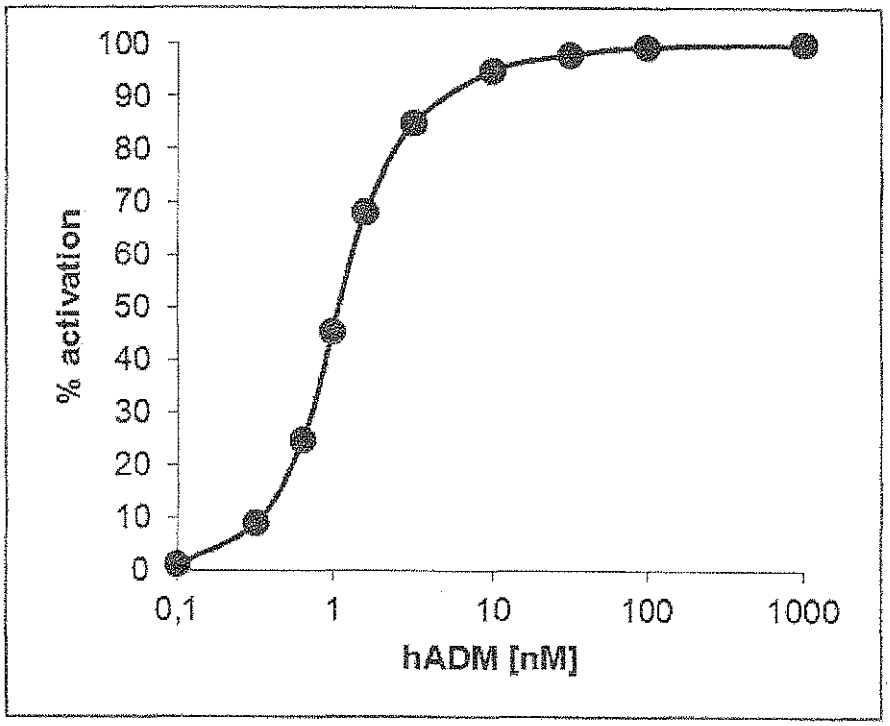



Fig. 3 b:

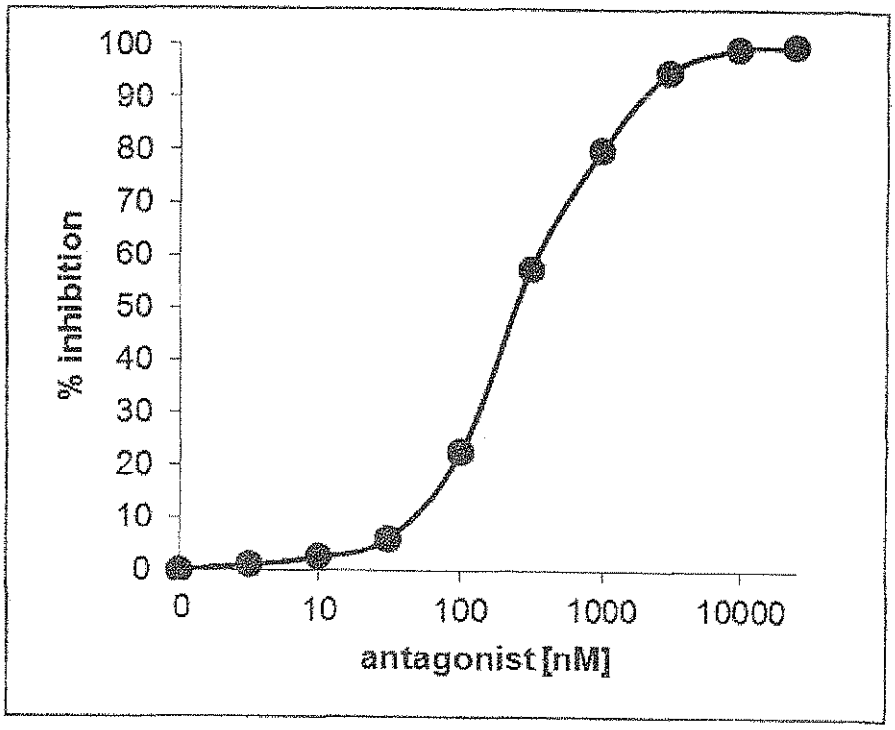

100
90
80
70
60
50
40
30
20
10
0
% inhibition
0
10
100
1000
10000
antagonist [nM]

Fig. 3 c:

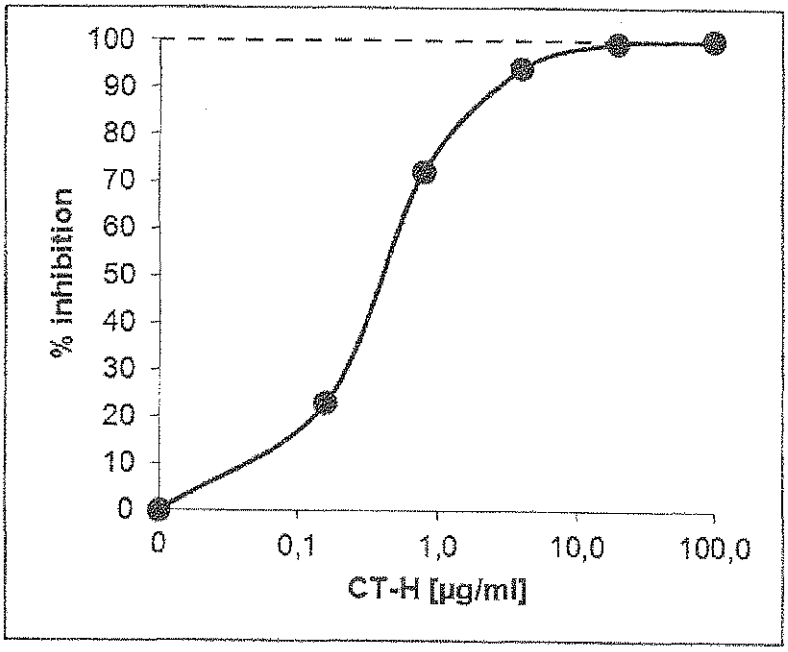

100
90
80
70
60
50
40
30
20
10
0
% inhibition
0
0,1
1,0
10,0
100,0
CT-H [µg/ml]

Fig. 3 d:

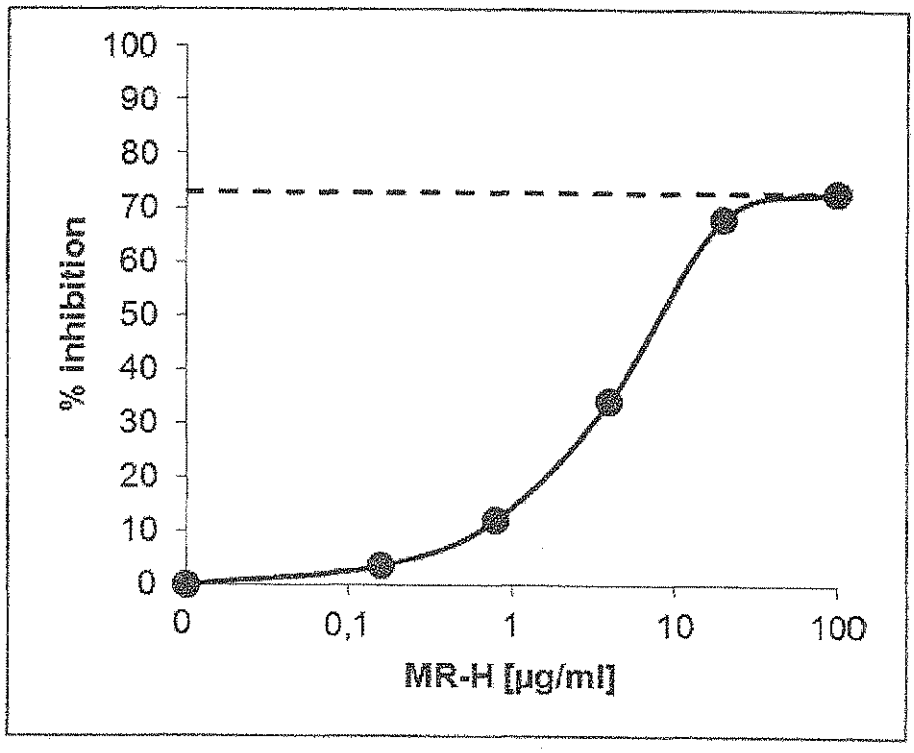

100
90
80
70
60
50
40
30
20
10
0
% inhibition
0
0,1
1
10
100
MR-H [µg/ml]

Fig. 3 e:

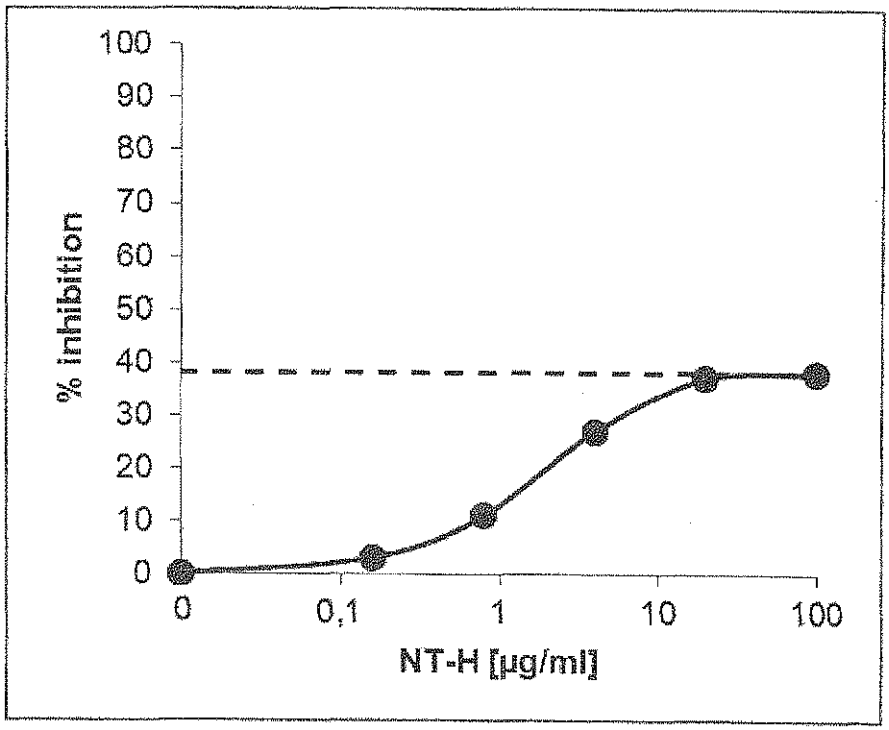

100
90
80
70
60
50
40
30
20
10
0
% inhibition
0
0,1
1
10
100
NT-H [µg/ml]

Fig. 3 f:

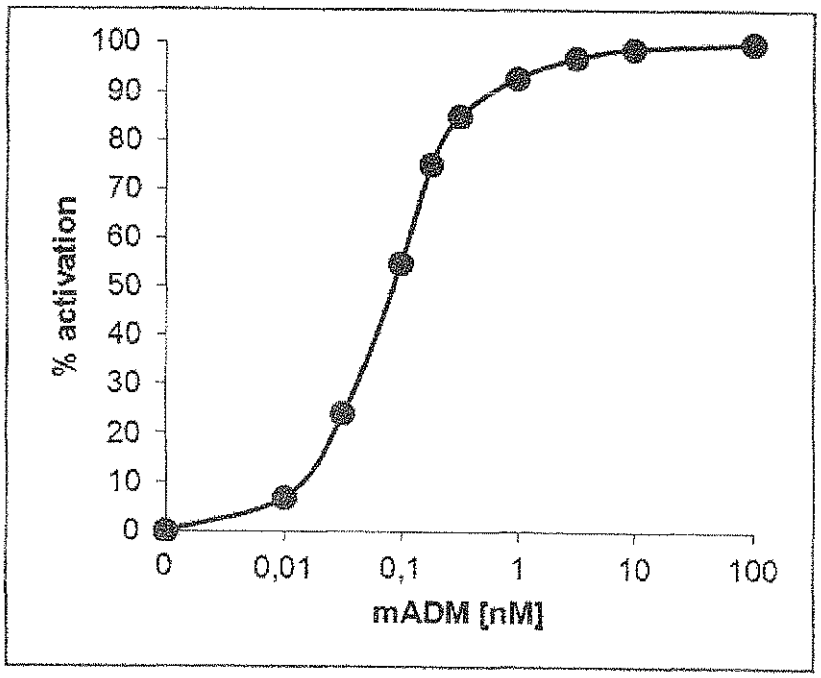

100
90
80
70
60
50
40
30
20
10
0
% activation
0
0,01
0,1
1
10
100
mADM [nM]

Fig. 3 g:

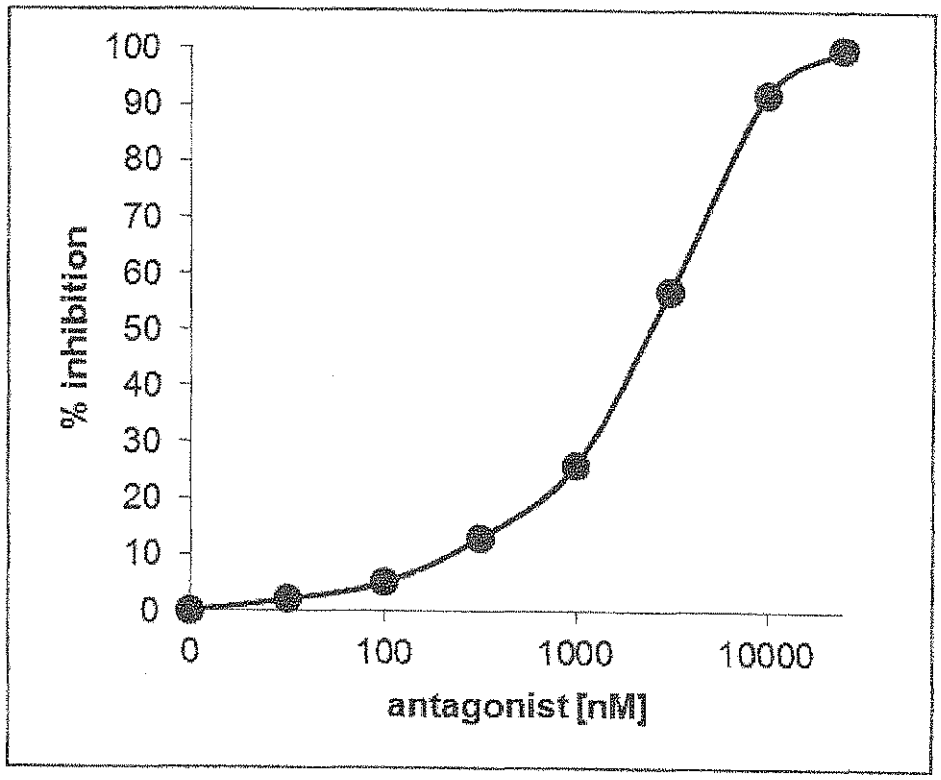

100
90
80
70
60
50
40
30
20
10
0
% inhibition
0
100
1000
10000
antagonist [nM]

Fig. 3 h:

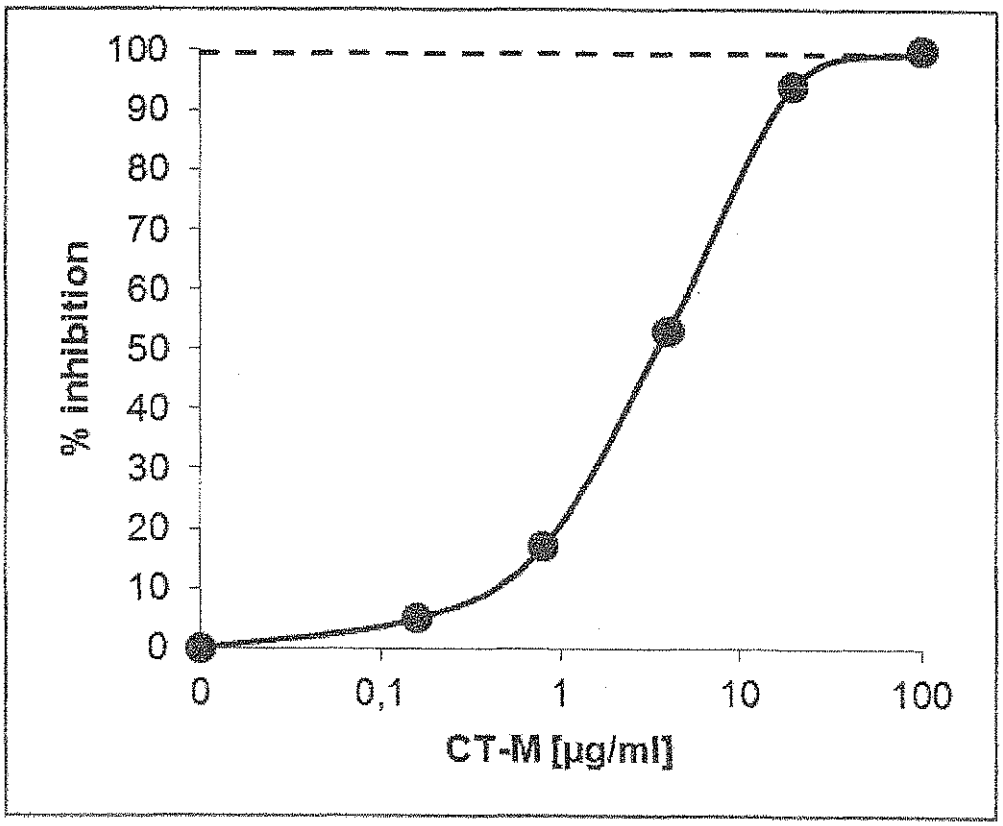

100
90
80
70
60
50
40
30
20
10
0
% inhibition
0
0,1
1
10
100
CT-M [µg/ml]

Fig. 3 i:

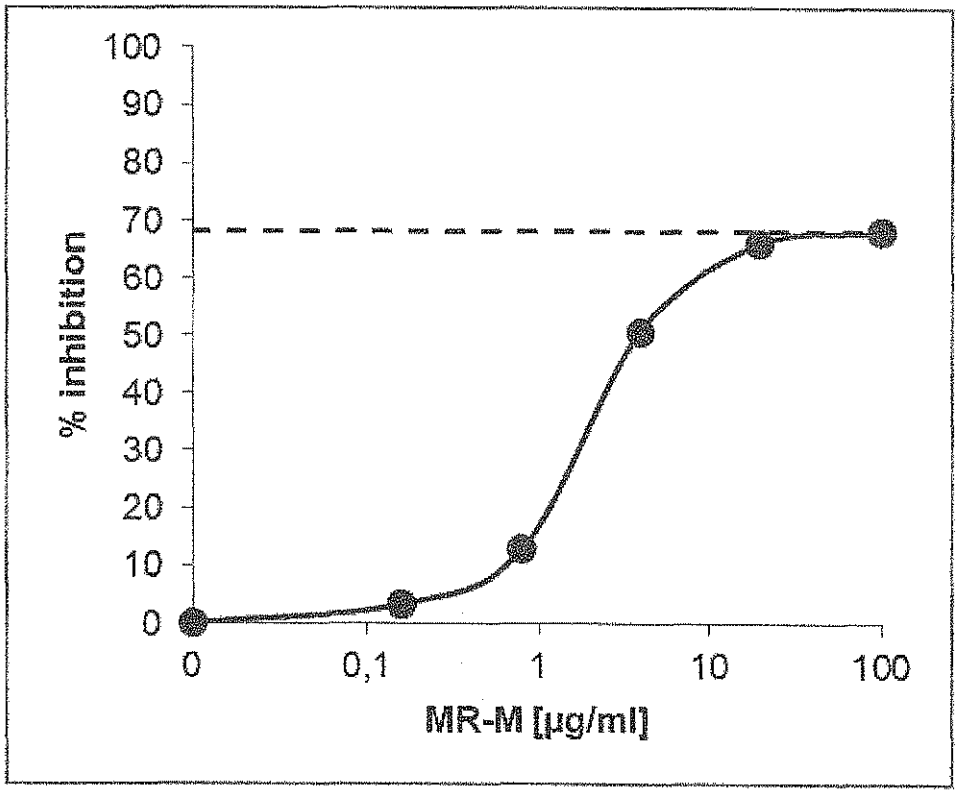

100
90
80
70
60
50
40
30
20
10
0
% inhibition
0
0,1
1
10
100
MR-M [µg/ml]

Fig. 3 j:

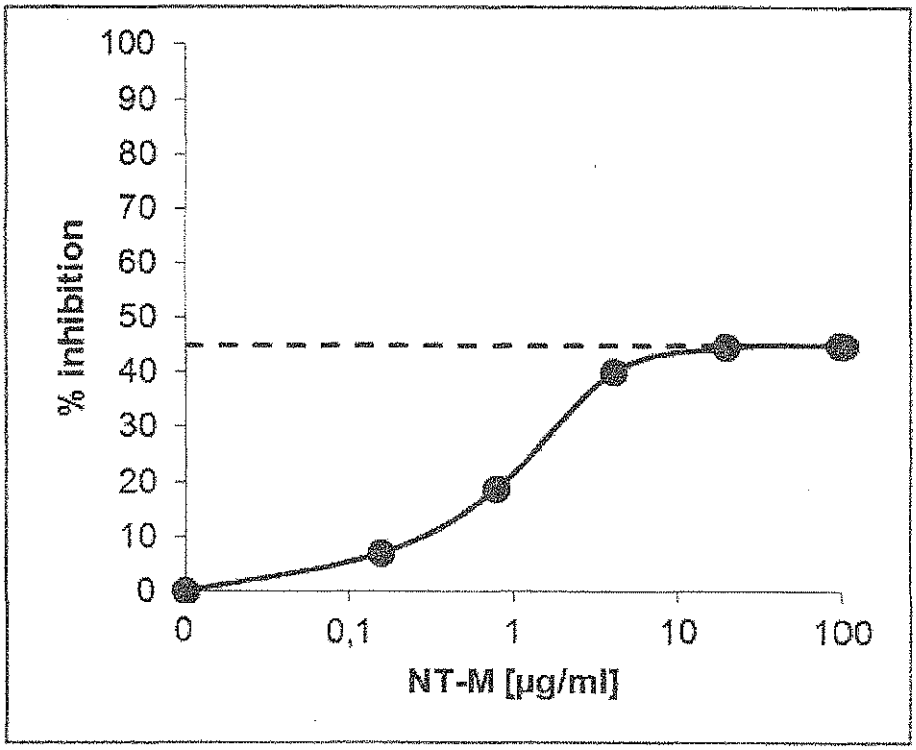

100
90
80
70
60
50
40
30
20
10
0
% Inhibition
0
0,1
1
10
100
NT-M [µg/ml]

Fig. 3 k:

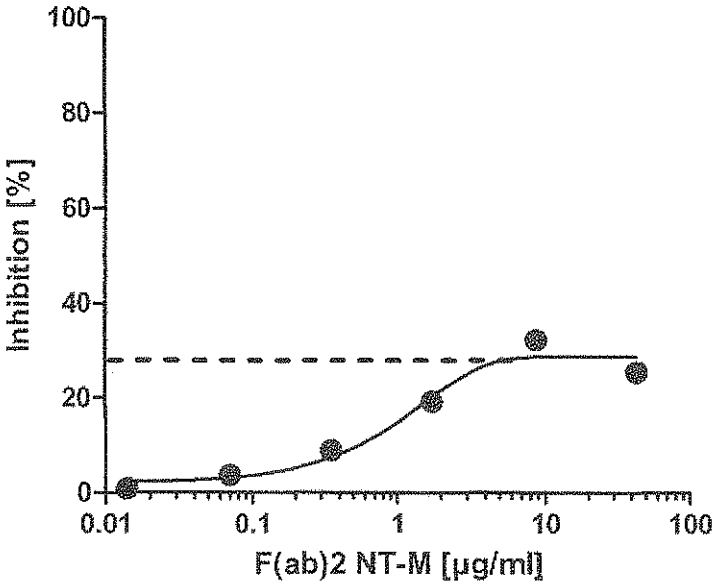

100
80
60
40
20
0
Inhibition [%]
0.01
0.1
1
10
100
F(ab)2 NT-M [µg/ml]

Fig. 3 l:

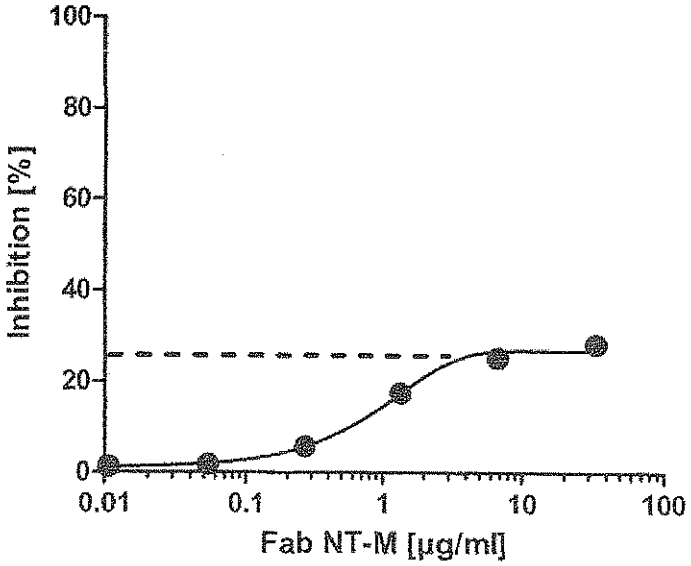

100
80
60
40
20
0
Inhibition [%]
0.01
0.1
1
10
100
Fab NT-M [µg/ml]

Fig. 4:

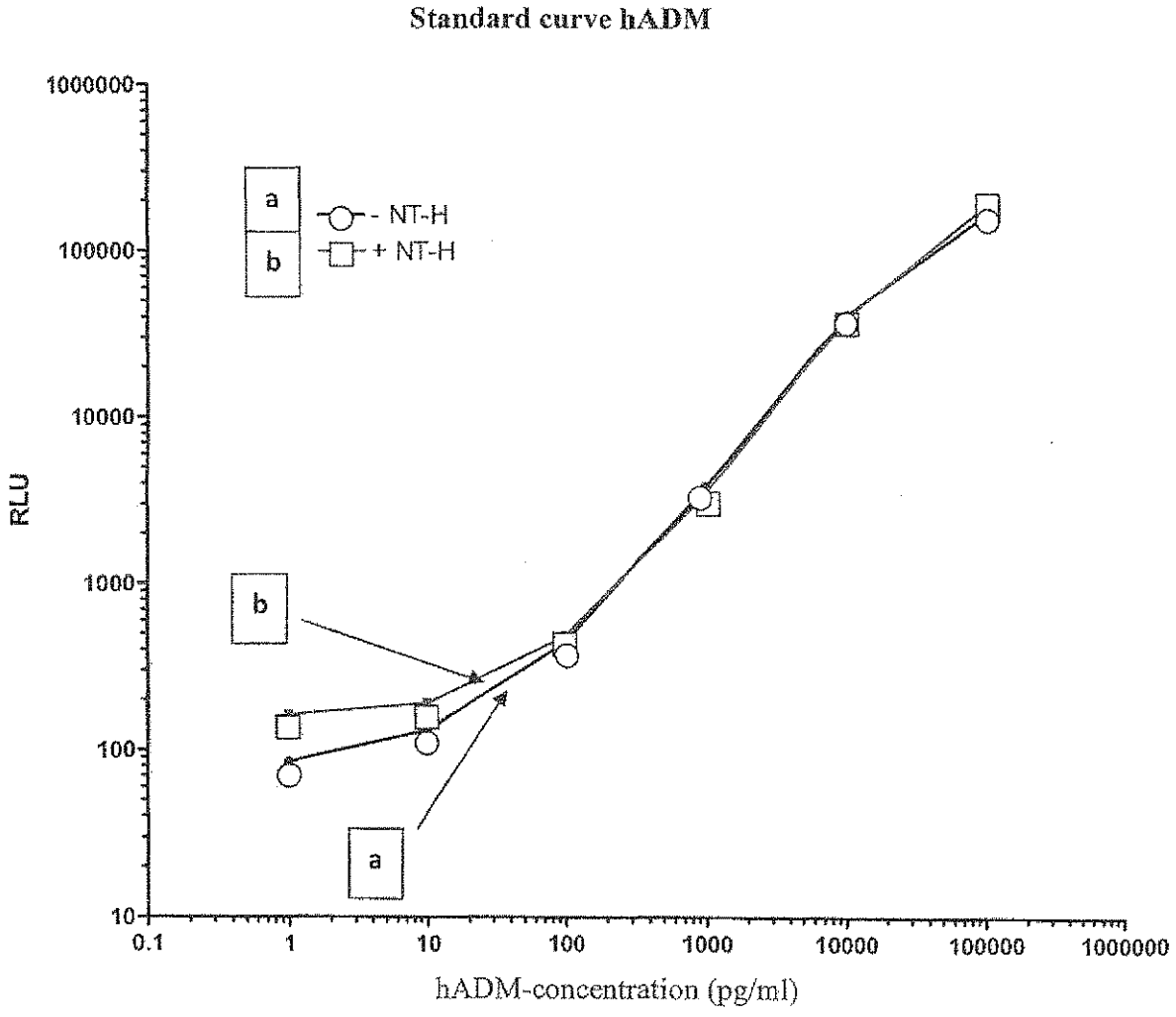
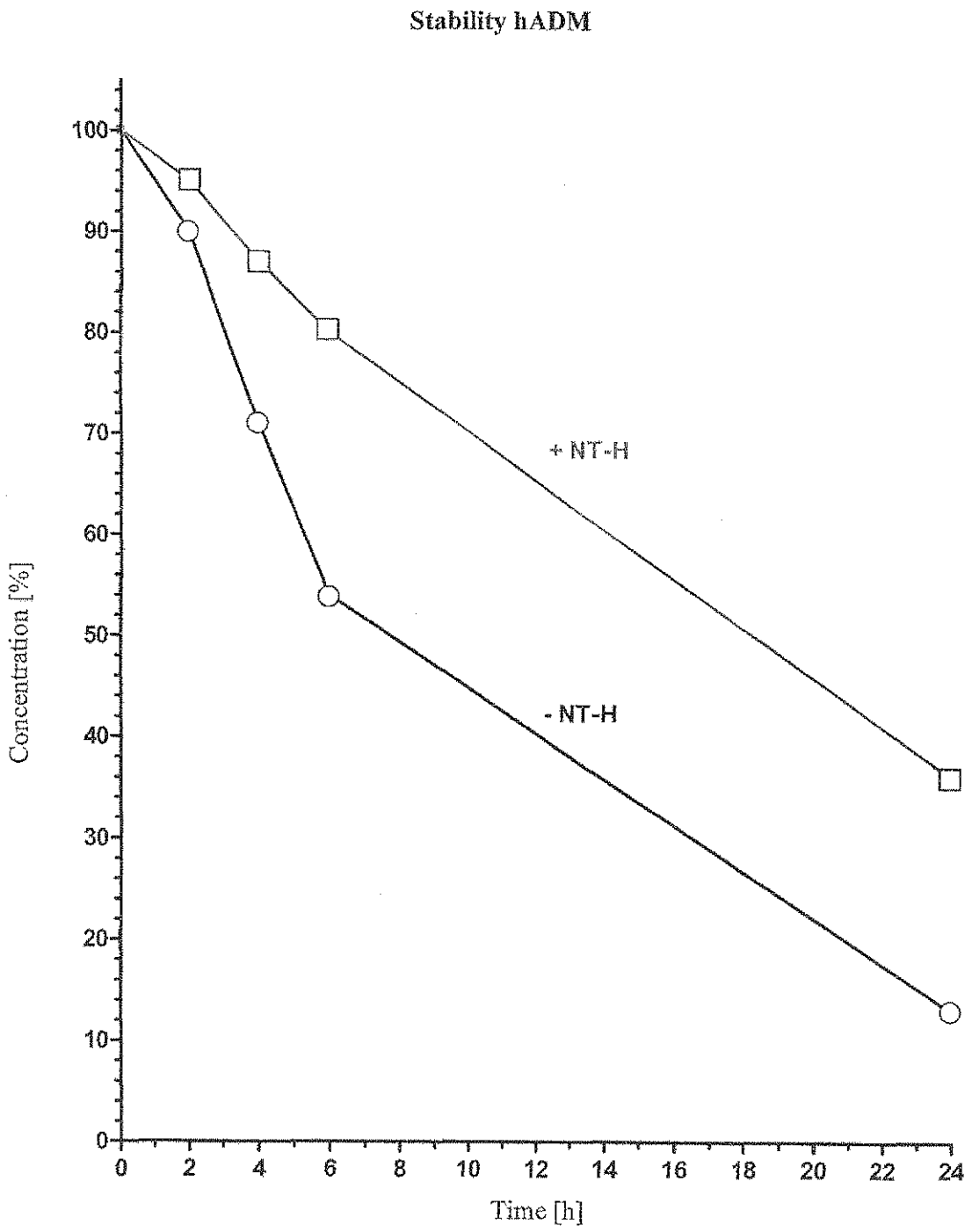

Standard curve hADM
1000000
100000
10000
1000
100
10
RLU
a
b
- NT-H
+ NT-H
b
a
0.1
1
10
100
1000
10000
100000
1000000
hADM-concentration (pg/ml)

Fig. 5:


Stability hADM
Concentration [%]
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Time [h]
+ NT-H
- NT-H

5

**Fig 6:**

**IGHV1-69*11:**
QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGRIIPILGT
ANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARYYYYYGMDVWGQGT
TVTVSS
**HB3:**
QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEILPGSGS
TNYNEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFDYWGQGTT
LTVSS

**Alignment (ClustalW2):** Identical amino acids are illustrated by stars; points indicate conservative changes.

```
IGHV1:

        QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGRIIPILGTANYAQKFQGR
        VTITADESTSTAYMELSSLRSEDTAVYYCARYYYYYGMDVWGQGTTVTVSS

HB3:

        QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEILPGSGSTNYNEKFKGK
        ATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFDYWGQGTTLTVSS

        **** *****: ***:***:****:* *** * *.**:* **:****:*.*:*  *::** :**:*:
        .***** *:.****:**** ***:*****:. * * *:* ******:****
```

Fig. 7

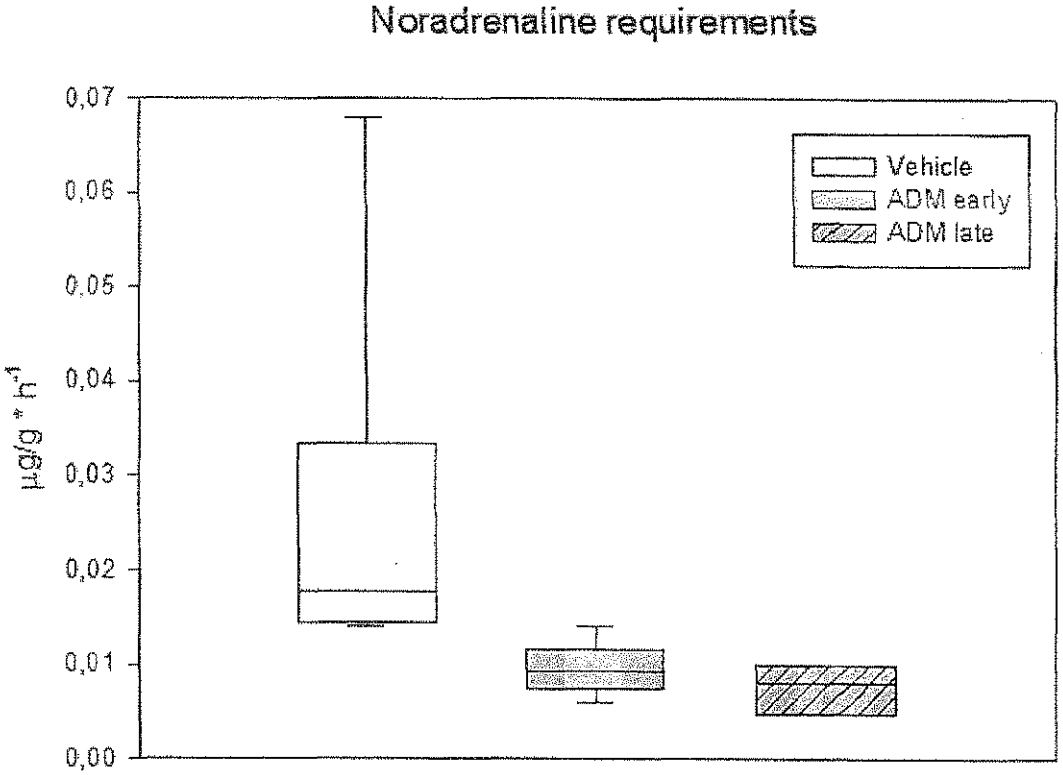

Noradrenaline requirements
0,07
0,06
0,05
0,04
0,03
0,02
0,01
0,00
µg/g * h-1
Vehicle
ADM early
ADM late

Fig. 8

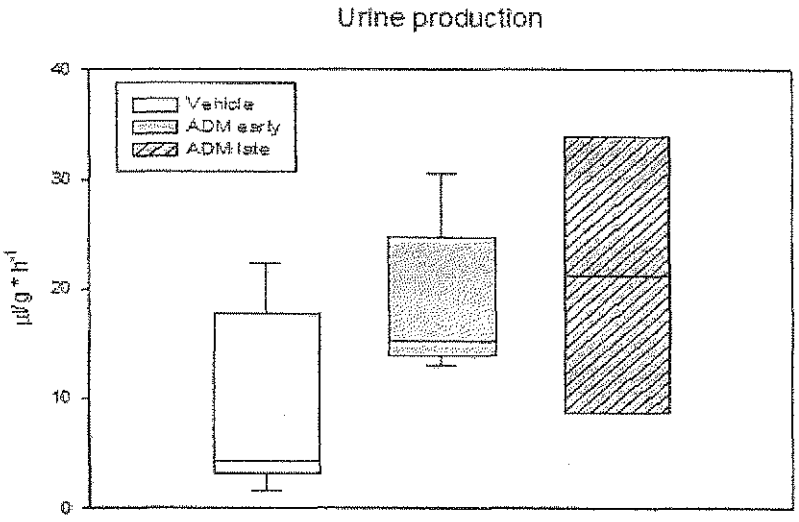

Urine production
40
30
20
10
0
µl/g * h-1
Vehicle
ADM early
ADM late

Fig. 9

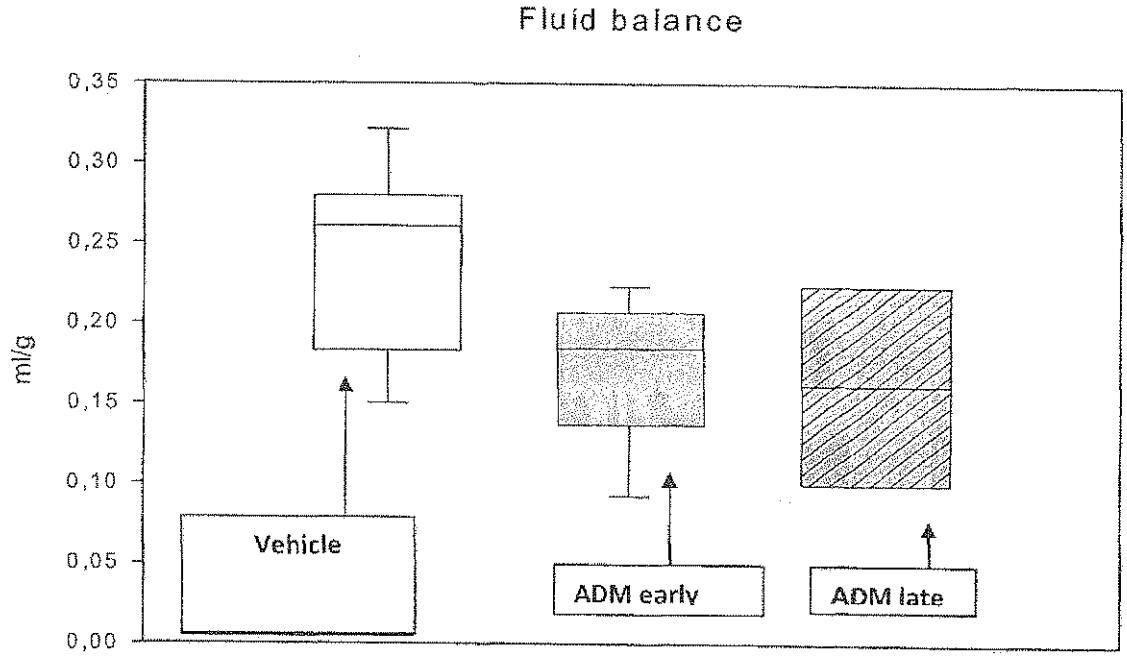

Fluid balance
ml/g
0,35
0,30
0,25
0,20
0,15
0,10
0,05
0,00
Vehicle
ADM early
ADM late

Fig. 10

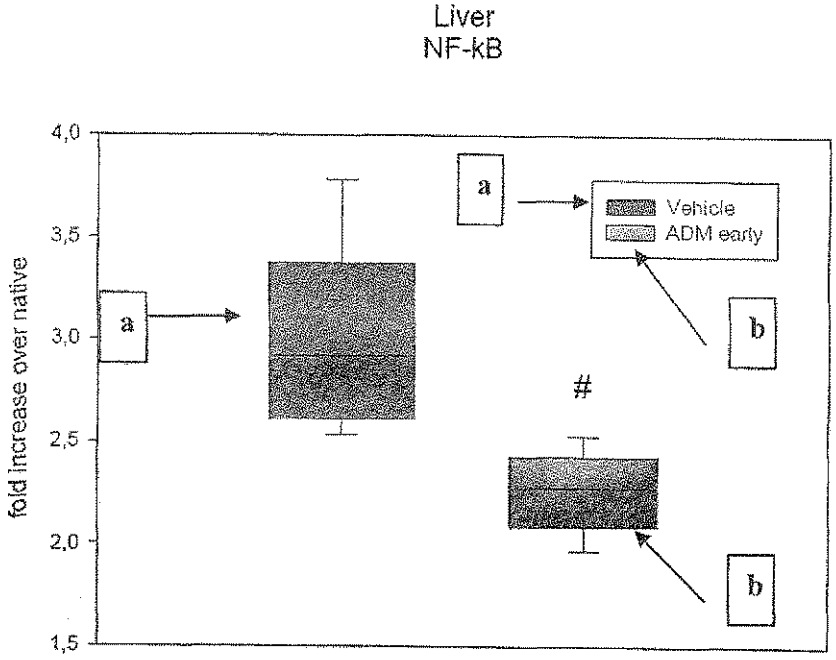

Liver
NF-kB
fold increase over native
4,0
3,5
3,0
2,5
2,0
1,5
a
a
b
b
#
Vehicle
ADM early

Fig. 11:

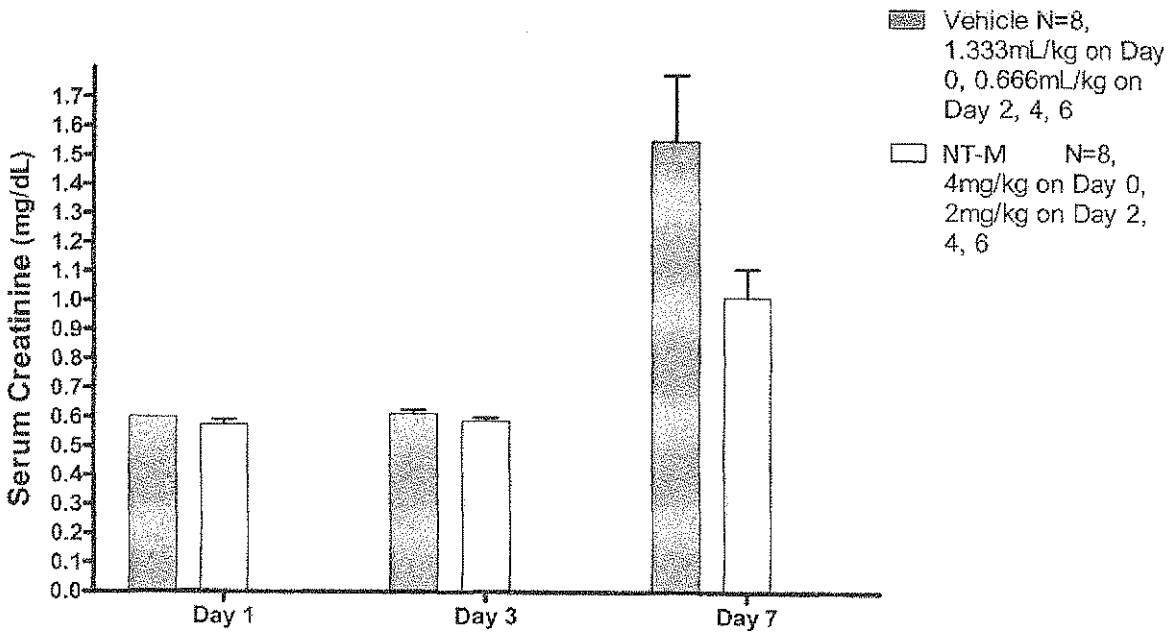

Serum Creatinine (mg/dL)
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Day 1
Day 3
Day 7
Vehicle N=8, 1.333mL/kg on Day 0, 0.666mL/kg on Day 2, 4, 6
NT-M N=8, 4mg/kg on Day 0, 2mg/kg on Day 2, 4, 6

Fig. 12:

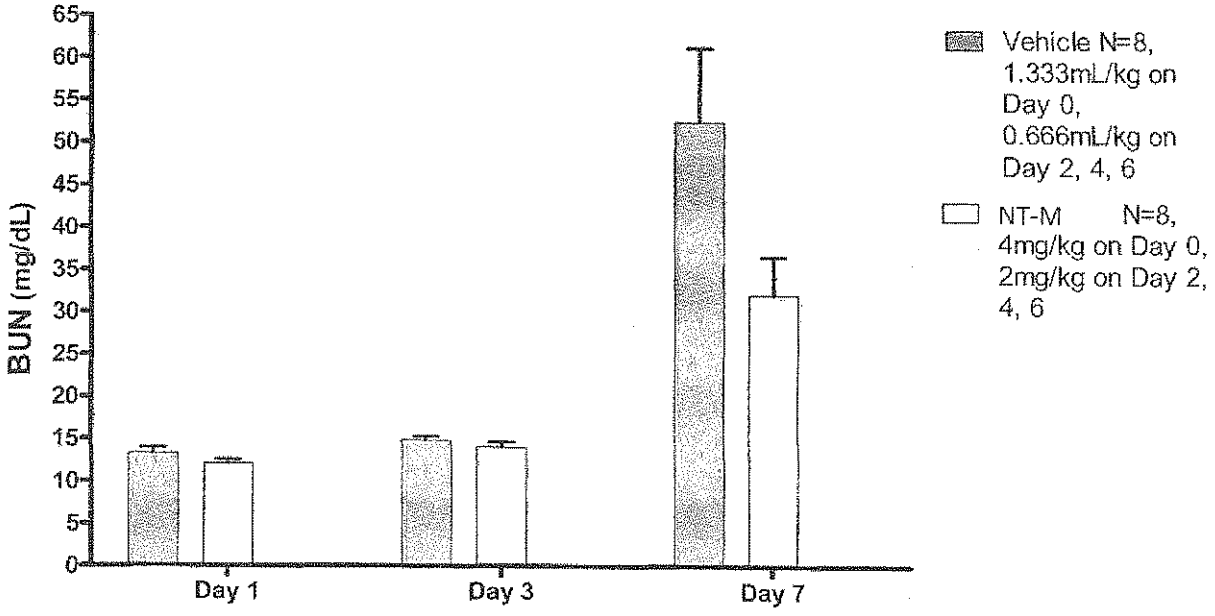

BUN (mg/dL)
65
60
55
50
45
40
35
30
25
20
15
10
5
0
Day 1
Day 3
Day 7
Vehicle N=8, 1.333mL/kg on Day 0, 0.666mL/kg on Day 2, 4, 6
NT-M N=8, 4mg/kg on Day 0, 2mg/kg on Day 2, 4, 6

Fig. 13:

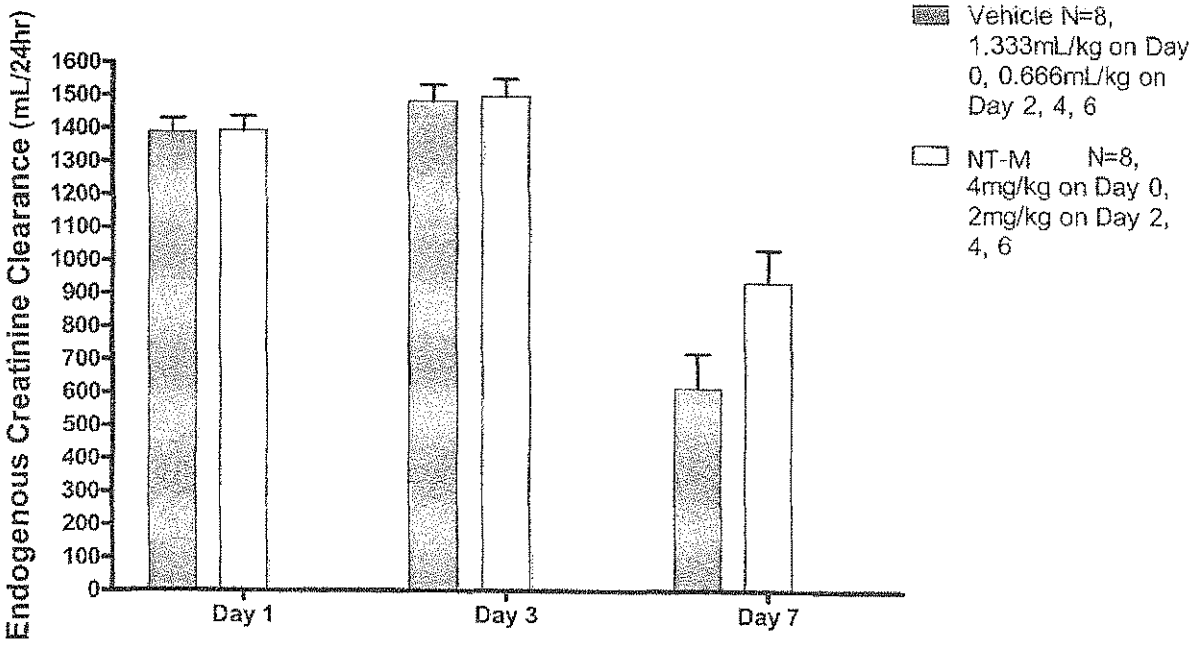

Endogenous Creatinine Clearance (mL/24hr)
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
Day 1
Day 3
Day 7
Vehicle N=8, 1.333mL/kg on Day 0, 0.666mL/kg on Day 2, 4, 6
NT-M N=8, 4mg/kg on Day 0, 2mg/kg on Day 2, 4, 6

Fig. 14:

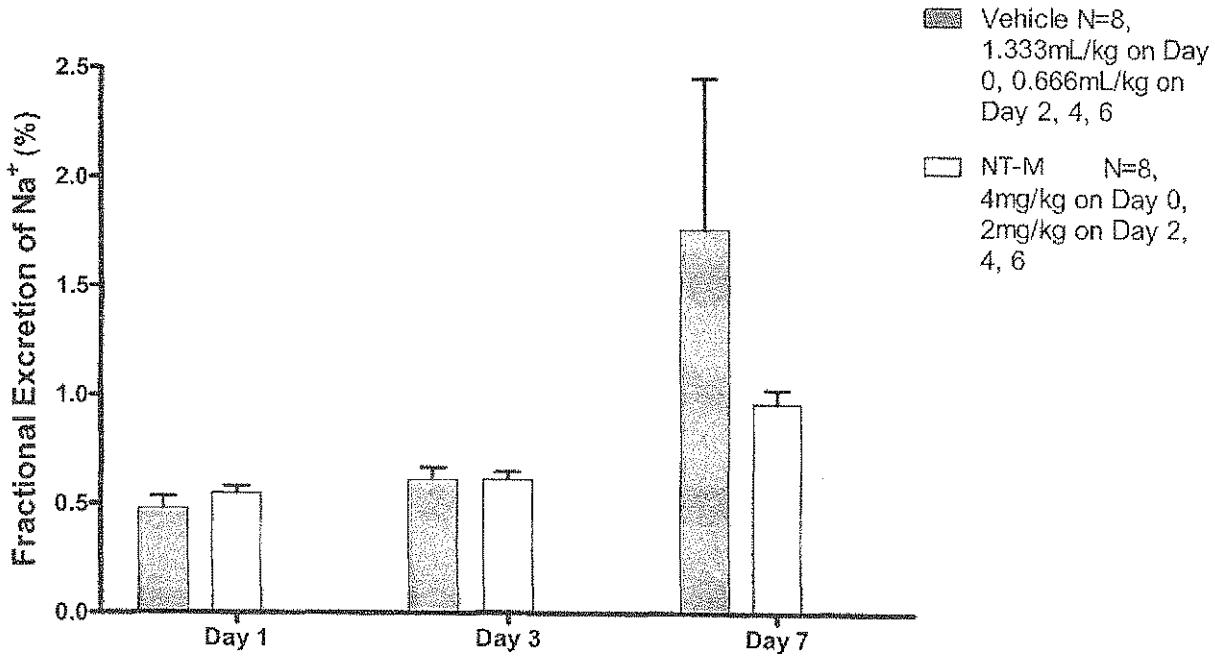

Fractional Excretion of $Na^+$ (%)
2.5
2.0
1.5
1.0
0.5
0.0
Day 1
Day 3
Day 7
Vehicle N=8, 1.333mL/kg on Day 0, 0.666mL/kg on Day 2, 4, 6
NT-M N=8, 4mg/kg on Day 0, 2mg/kg on Day 2, 4, 6

**Fig. 15:**

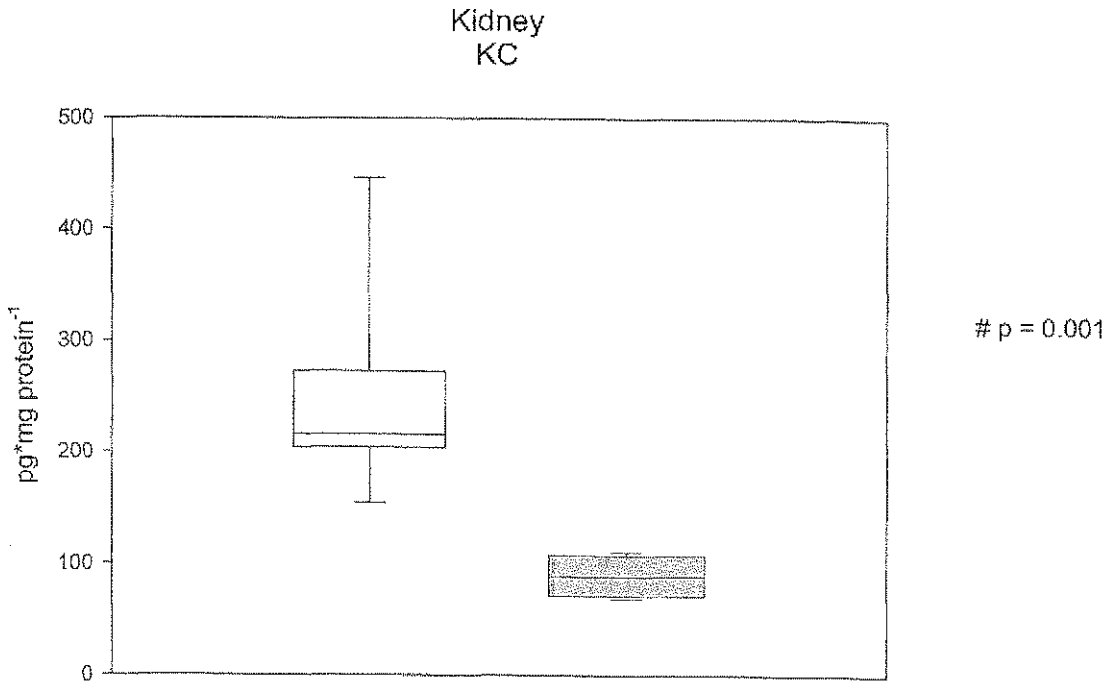

Kidney
KC
500
400
300
200
100
0
pg*mg protein-1
# p = 0.001

**Fig. 16:**

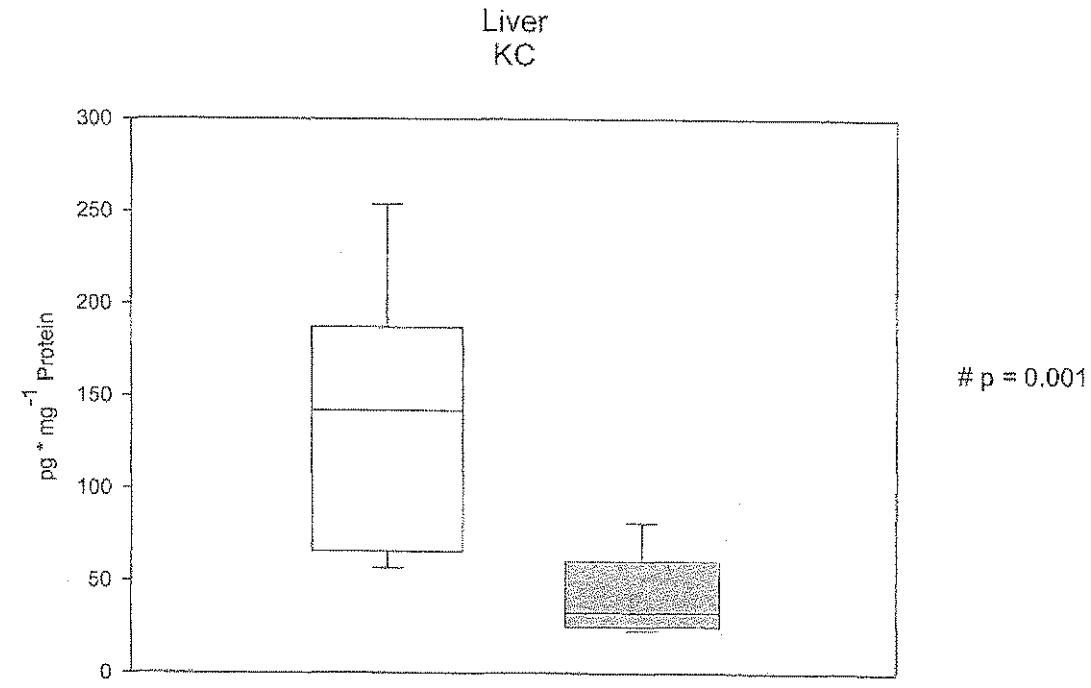
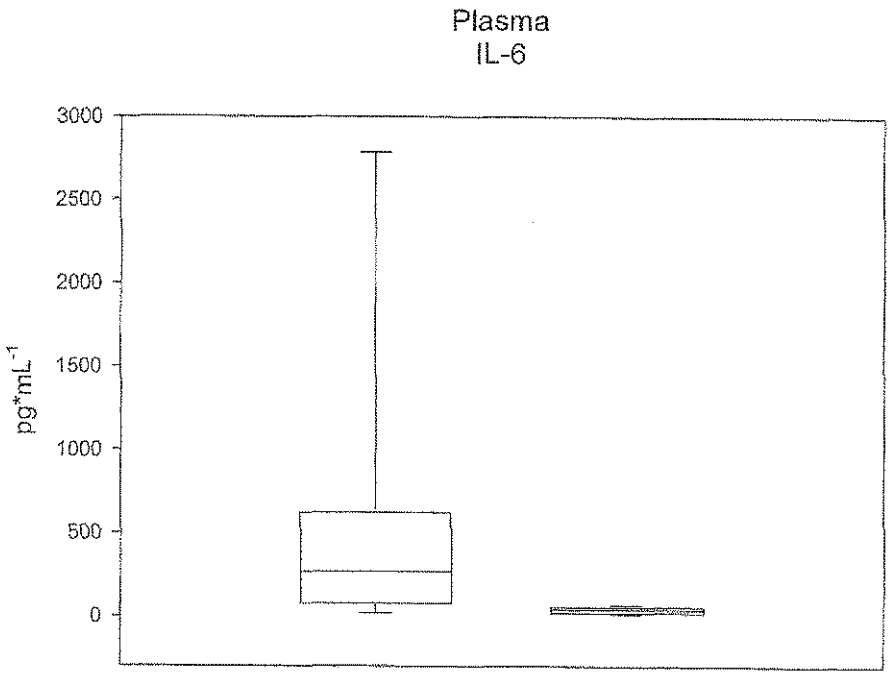
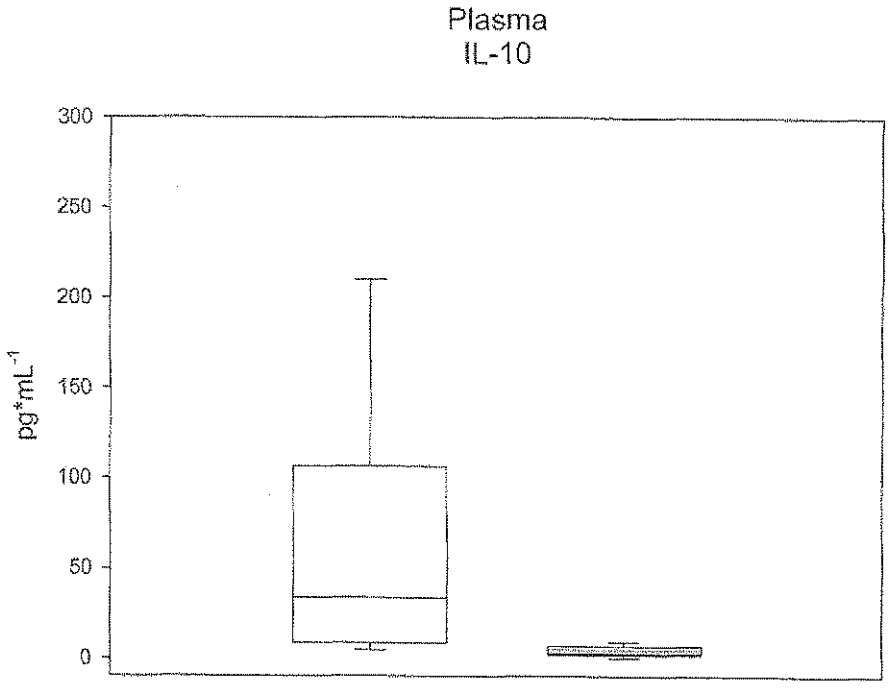

Liver
KC
300
250
200
150
100
50
0
pg * mg -1 Protein
# p = 0.001

Fig. 17:




# p = 0.017

Fig. 18:




# p = 0.002

**Fig. 19:**

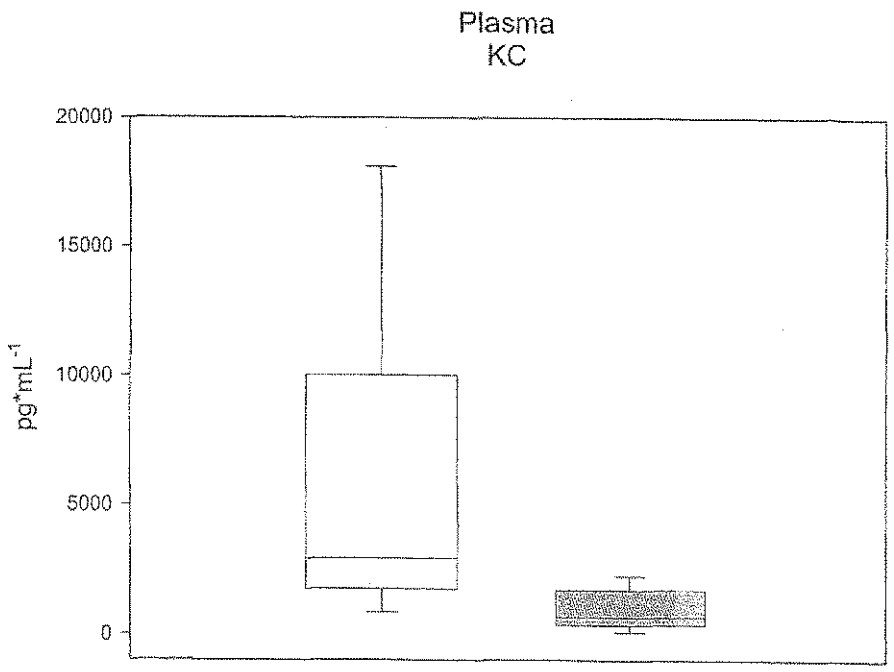

Plasma
KC
20000
15000
10000
5000
0
pg*mL-1
# p = 0.004

**Fig. 20:**

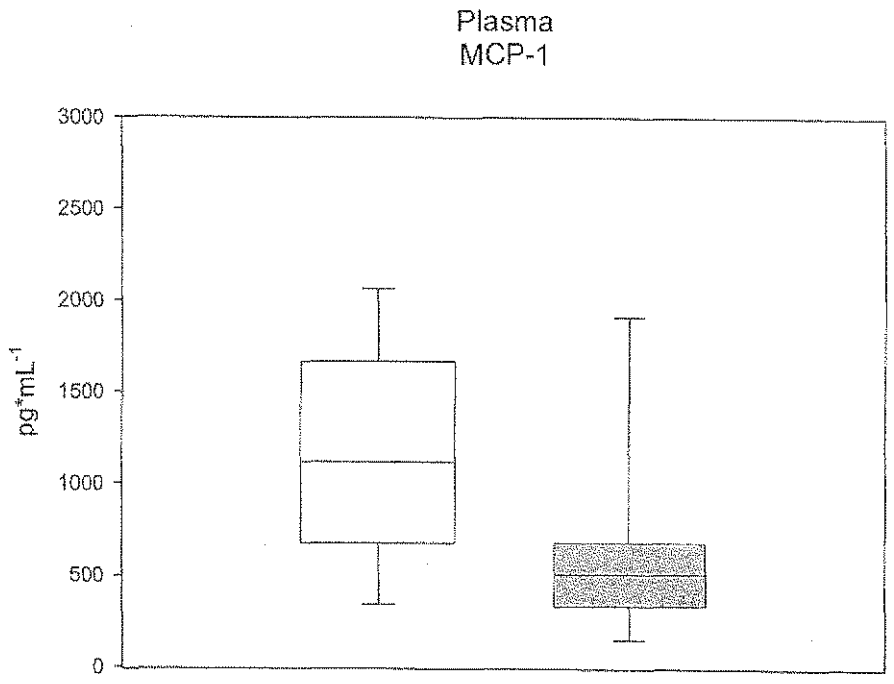

Plasma
MCP-1
3000
2500
2000
1500
1000
500
0
pg*mL-1
# p = 0.027

**Fig. 21:**

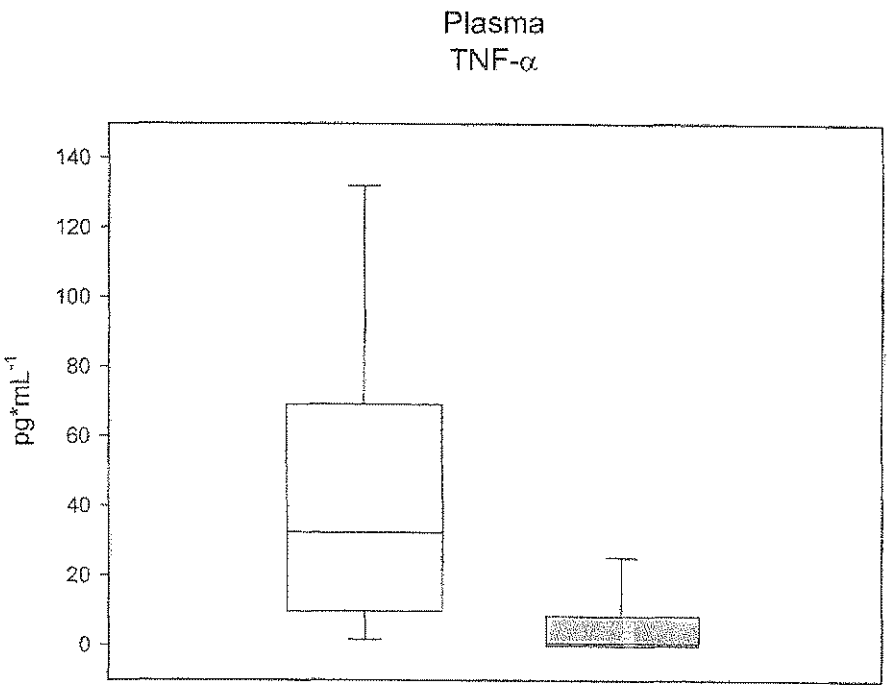

Plasma
TNF-α
pg*mL-1
140
120
100
80
60
40
20
0
# p = 0.005

**Fig. 22:**

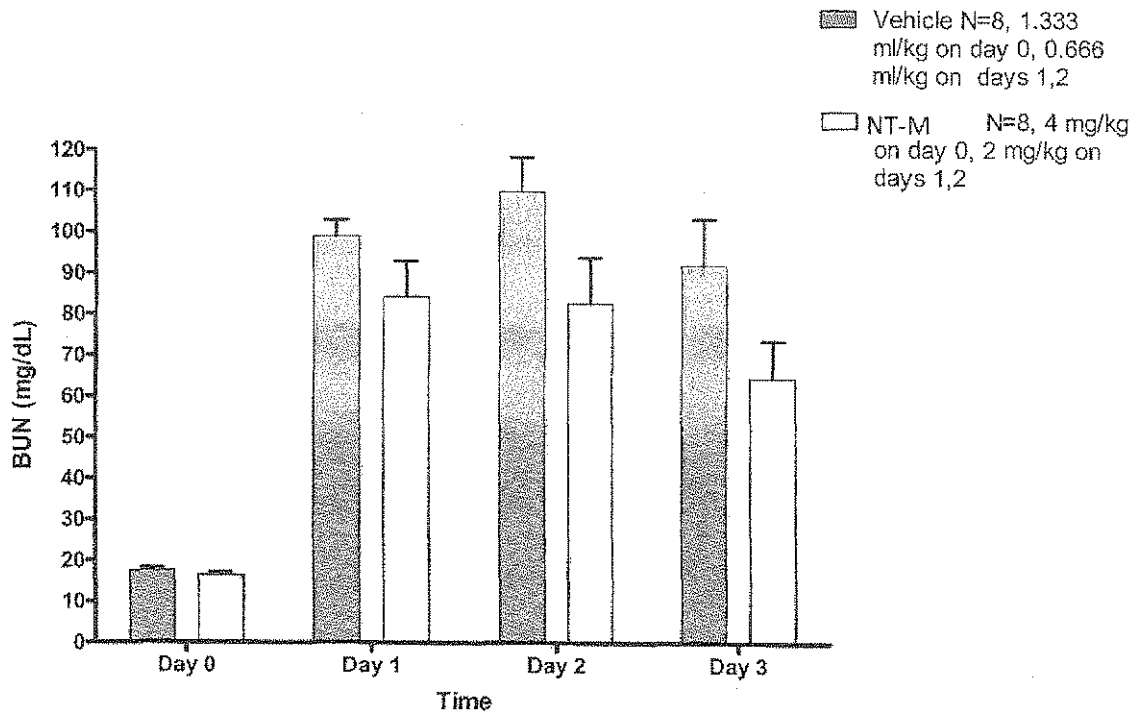

Vehicle N=8, 1.333 ml/kg on day 0, 0.666 ml/kg on days 1,2
NT-M N=8, 4 mg/kg on day 0, 2 mg/kg on days 1,2
BUN (mg/dL)
120
110
100
90
80
70
60
50
40
30
20
10
0
Day 0
Day 1
Day 2
Day 3
Time

Fig. 23:

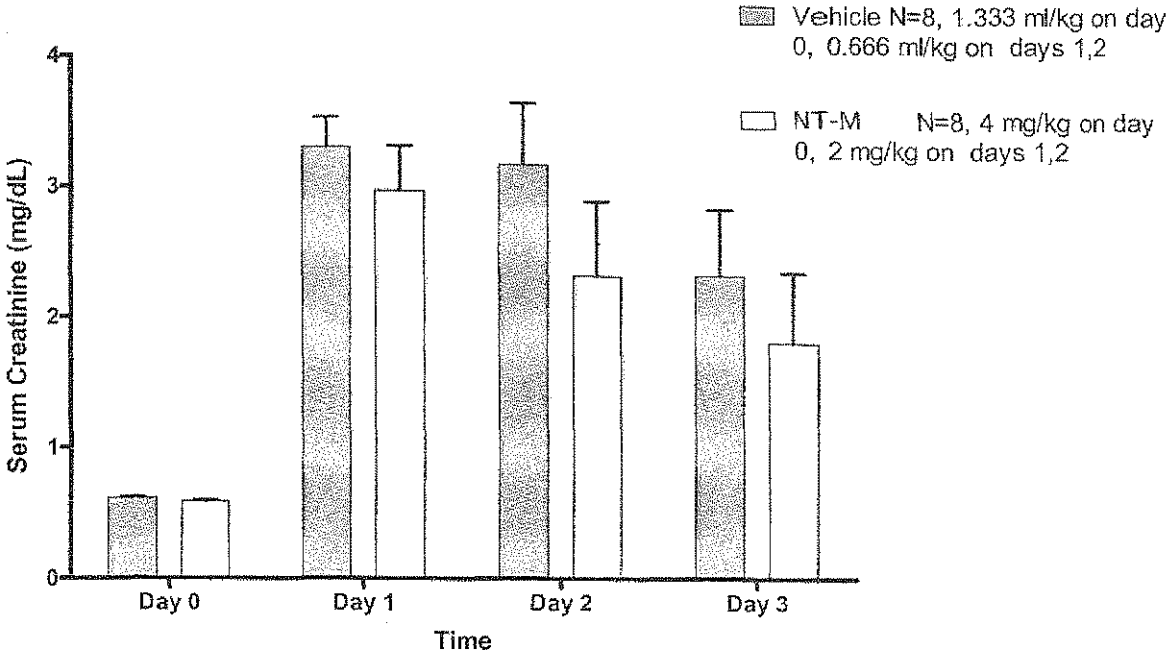
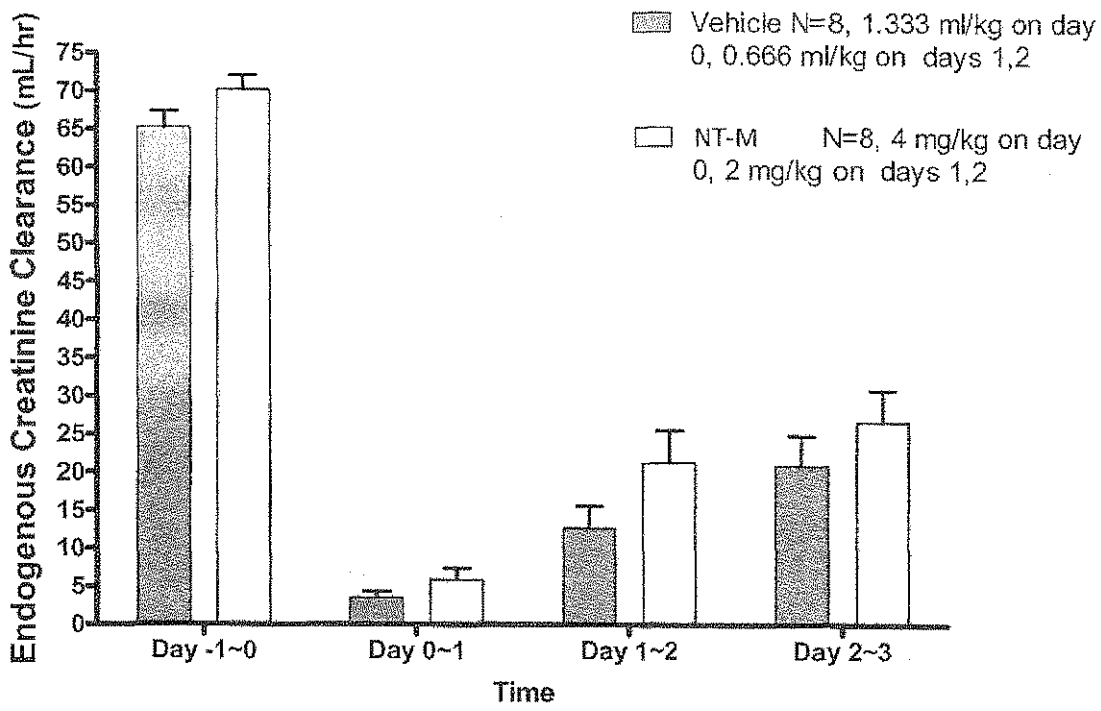

Vehicle N=8, 1.333 ml/kg on day 0, 0.666 ml/kg on days 1,2
NT-M N=8, 4 mg/kg on day 0, 2 mg/kg on days 1,2
Serum Creatinine (mg/dL)
0
1
2
3
4
Day 0
Day 1
Day 2
Day 3
Time

Fig. 24:


Vehicle N=8, 1.333 ml/kg on day 0, 0.666 ml/kg on days 1,2
NT-M N=8, 4 mg/kg on day 0, 2 mg/kg on days 1,2
Endogenous Creatinine Clearance (mL/hr)
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
Day -1~0
Day 0~1
Day 1~2
Day 2~3
Time