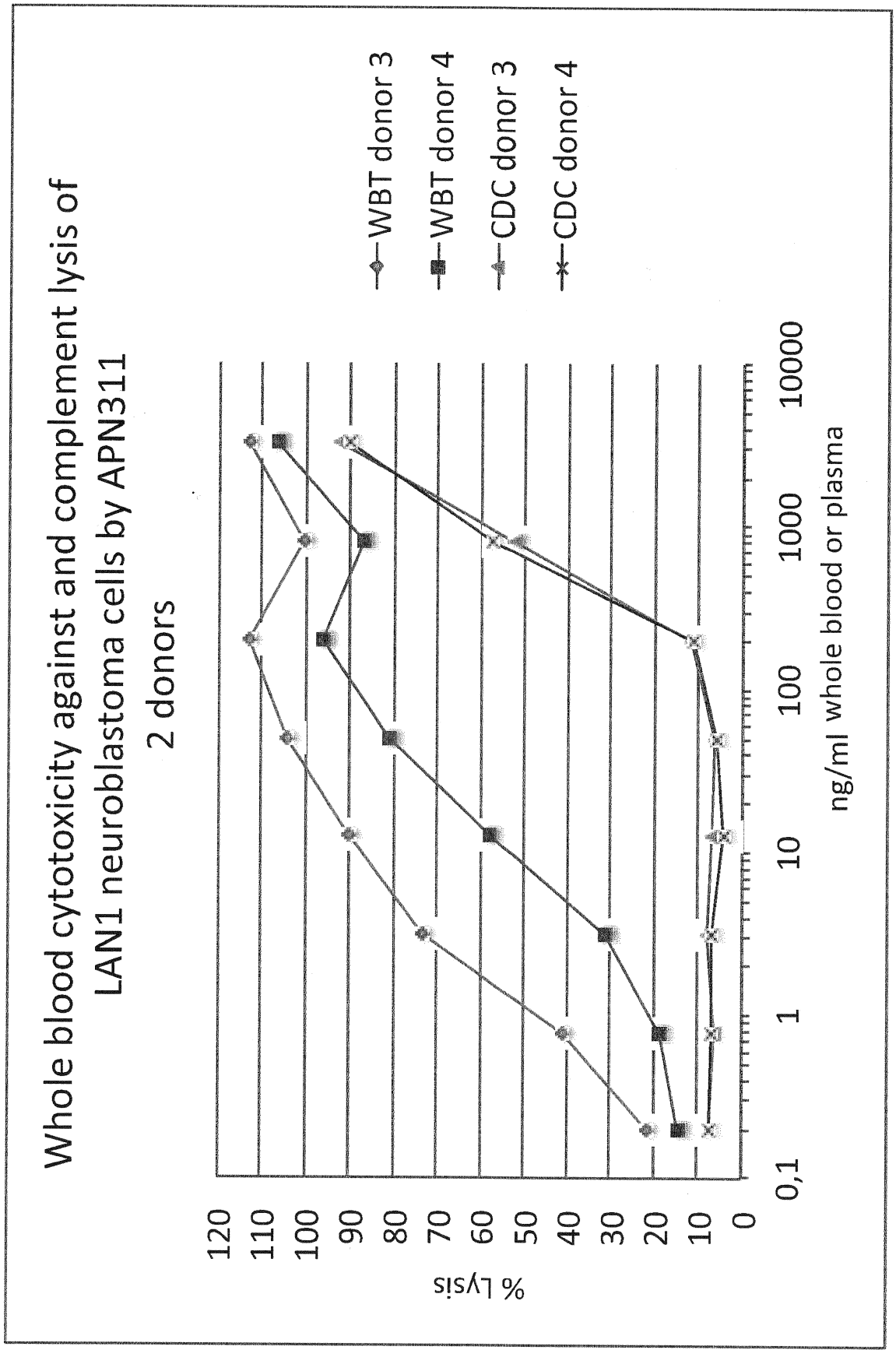

Whole blood cytotoxicity against and complement lysis of LAN1 neuroblastoma cells by APN311
2 donors
WBT donor 3
WBT donor 4
CDC donor 3
CDC donor 4
% Lysis
120
110
100
90
80
70
60
50
40
30
20
10
0
0,1
1
10
100
1000
10000
ng/ml whole blood or plasma

Fig. 1

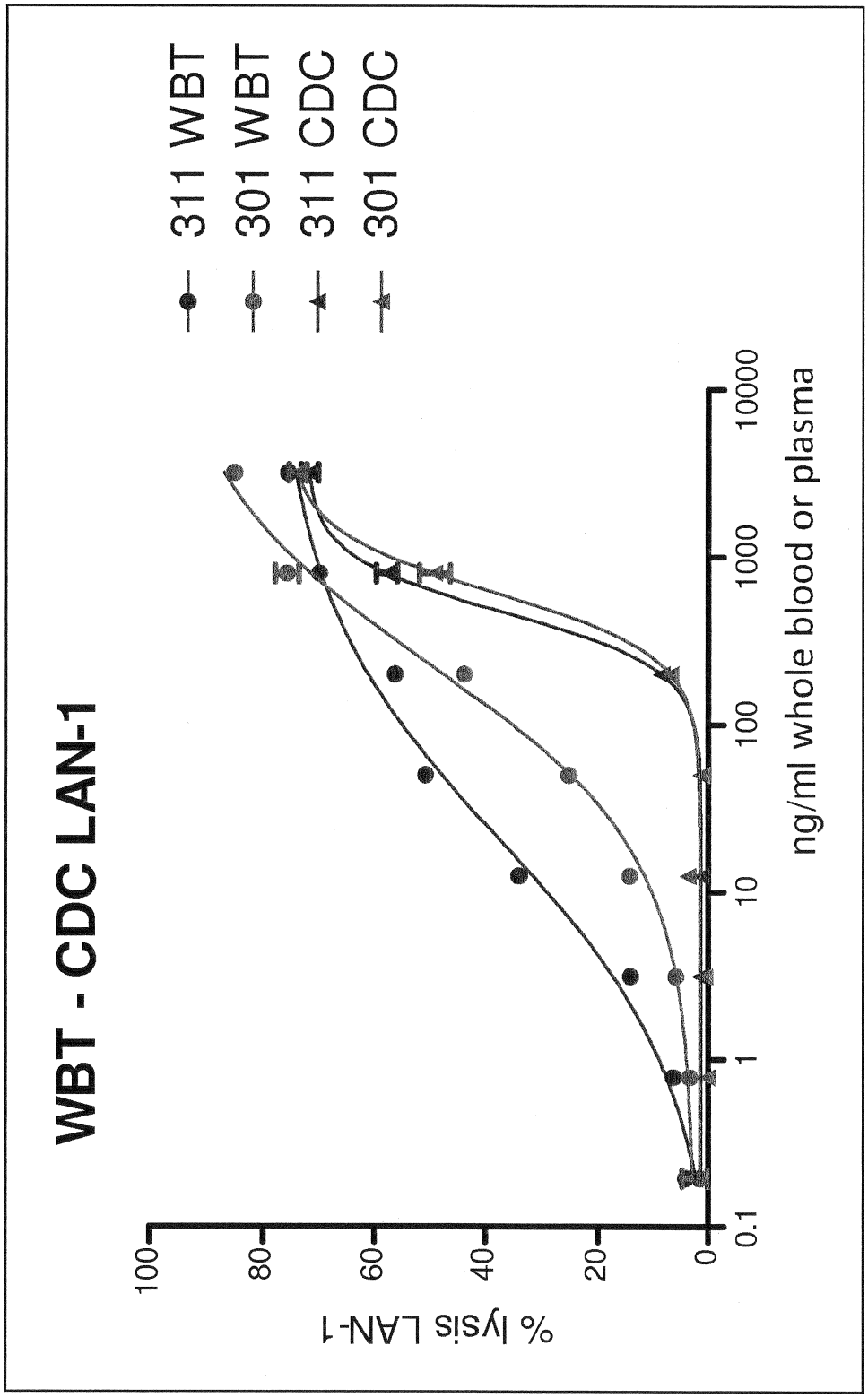

WBT - CDC LAN-1
311 WBT
301 WBT
311 CDC
301 CDC
% lysis LAN-1
100
80
60
40
20
0
0.1
1
10
100
1000
10000
ng/ml whole blood or plasma

Fig. 2

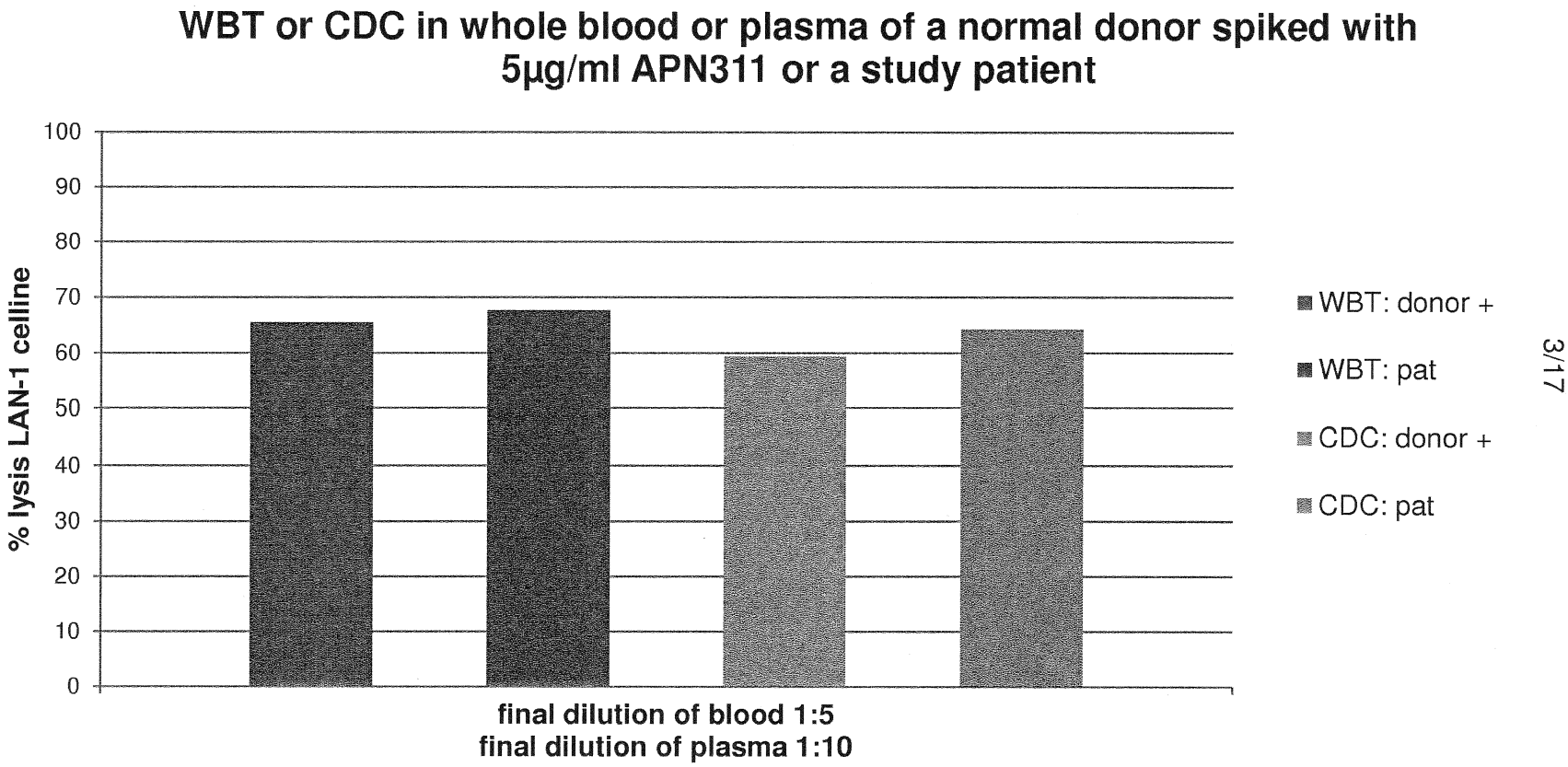

WBT or CDC in whole blood or plasma of a normal donor spiked with 5µg/ml APN311 or a study patient
% lysis LAN-1 celline
100
90
80
70
60
50
40
30
20
10
0
final dilution of blood 1:5
final dilution of plasma 1:10
WBT: donor +
WBT: pat
CDC: donor +
CDC: pat

Fig. 3

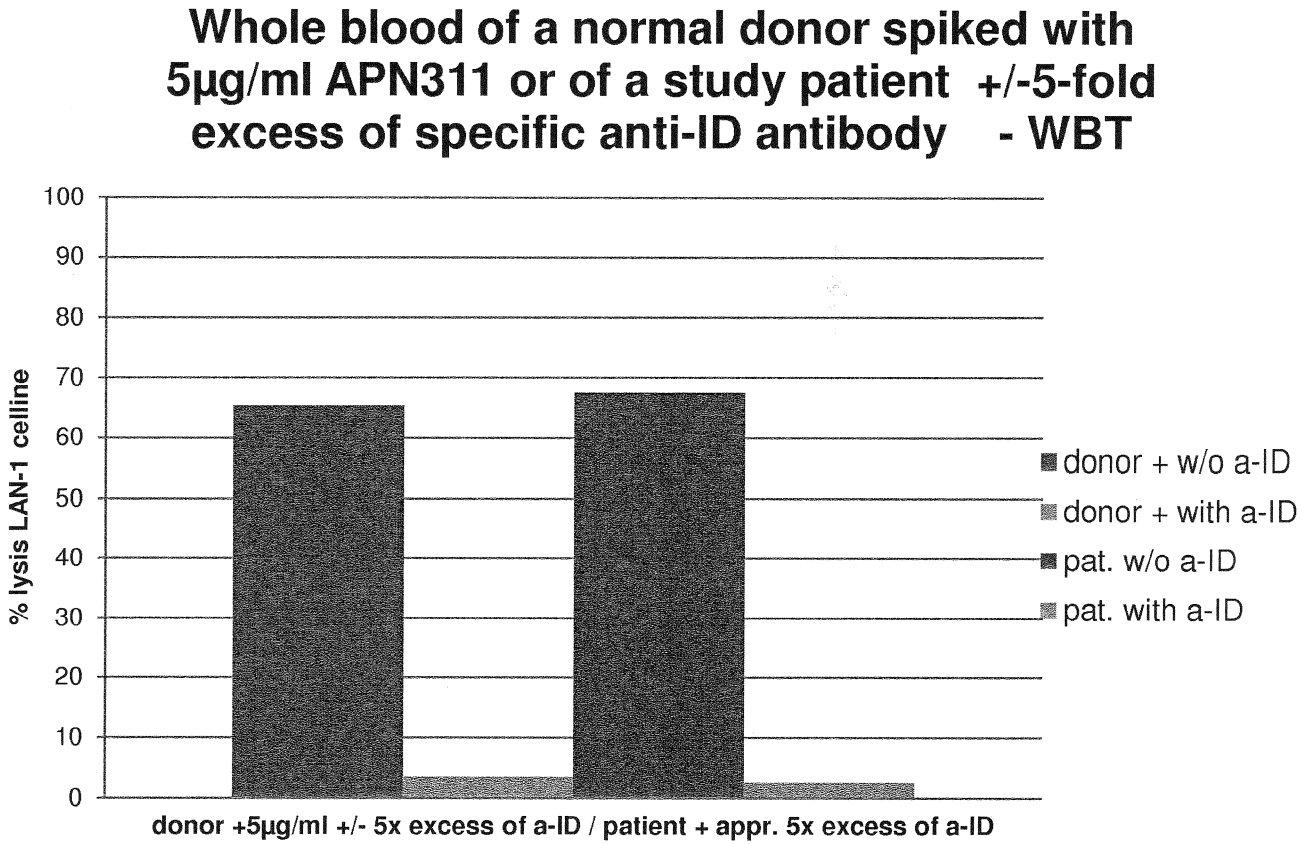

Whole blood of a normal donor spiked with 5µg/ml APN311 or of a study patient +/-5-fold excess of specific anti-ID antibody - WBT
% lysis LAN-1 celline
100
90
80
70
60
50
40
30
20
10
0
donor +5µg/ml +/- 5x excess of a-ID / patient + appr. 5x excess of a-ID
donor + w/o a-ID
donor + with a-ID
pat. w/o a-ID
pat. with a-ID

Fig. 4

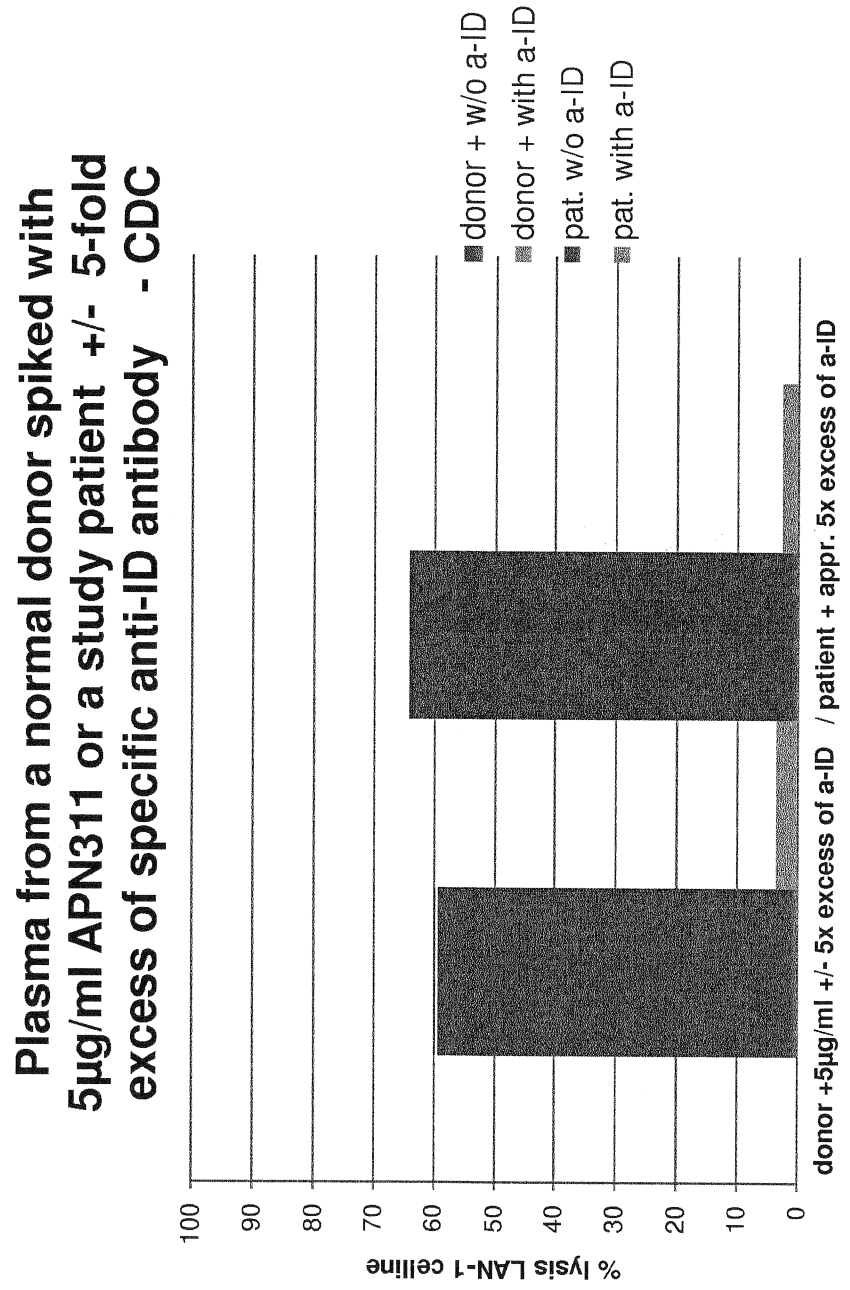

Plasma from a normal donor spiked with 5µg/ml APN311 or a study patient +/- 5-fold excess of specific anti-ID antibody - CDC
% lysis LAN-1 cellline
100
90
80
70
60
50
40
30
20
10
0
donor + w/o a-ID
donor + with a-ID
pat. w/o a-ID
pat. with a-ID
donor +5µg/ml +/- 5x excess of a-ID / patient + appr. 5x excess of a-ID

Fig. 5

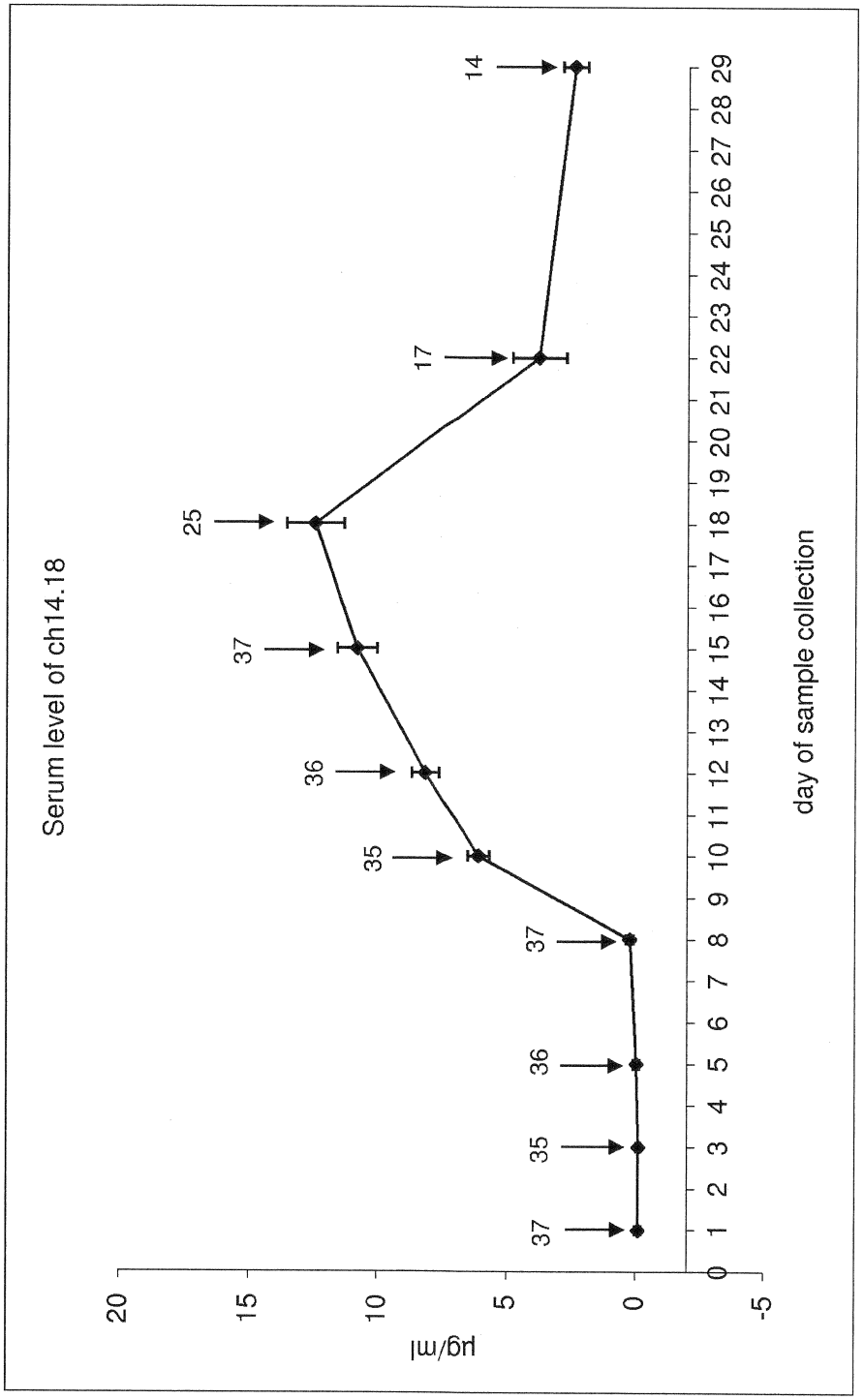

Serum level of ch14.18
μg/ml
20
15
10
5
0
-5
day of sample collection
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
37
35
36
37
25
37
36
35
37
17
14

Fig. 6

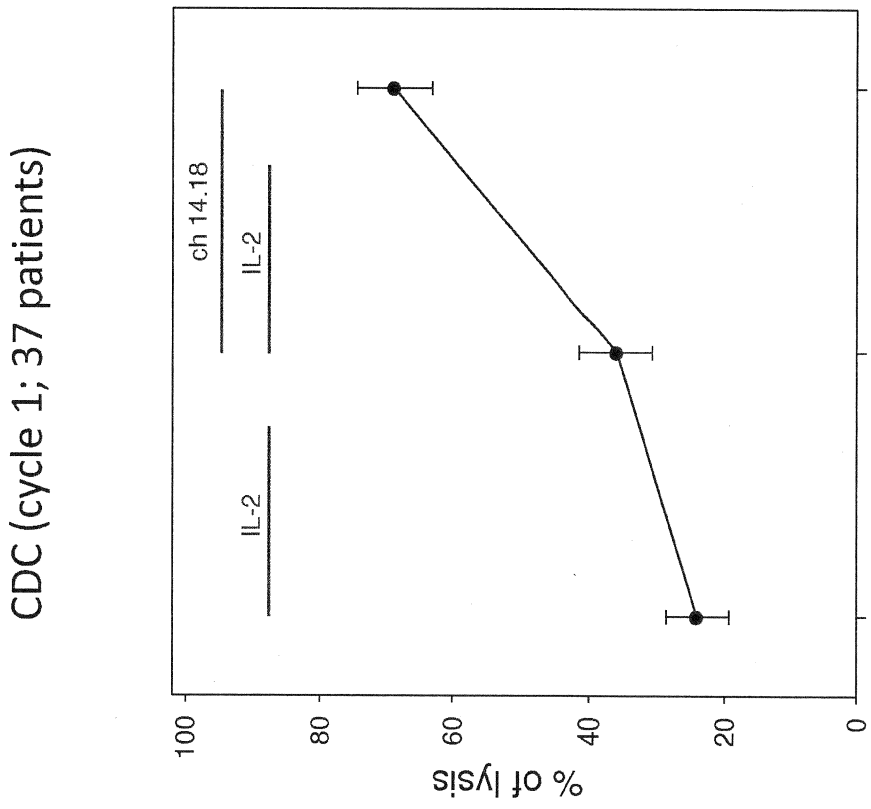

CDC (cycle 1; 37 patients)
% of lysis
100
80
60
40
20
0
ch 14.18
IL-2
IL-2
1
8
15
day of therapy

Fig. 7

Treatment schedule

ch14.18/CHO	100 mg/m²/cycle, 10 day: continuous infusion i.v.
aldesleukin (IL2)	60 x 10^6 IU/m²/cycle, 10 days: two 5 day periods, 6 x 10^6 IU/ m²/day s.c.
13-cis retinoid acid	2240 mg/m²/cycle, 14 days: 14 x 160 mg/m²/day p.o.

5 cycles; 35 day intervals

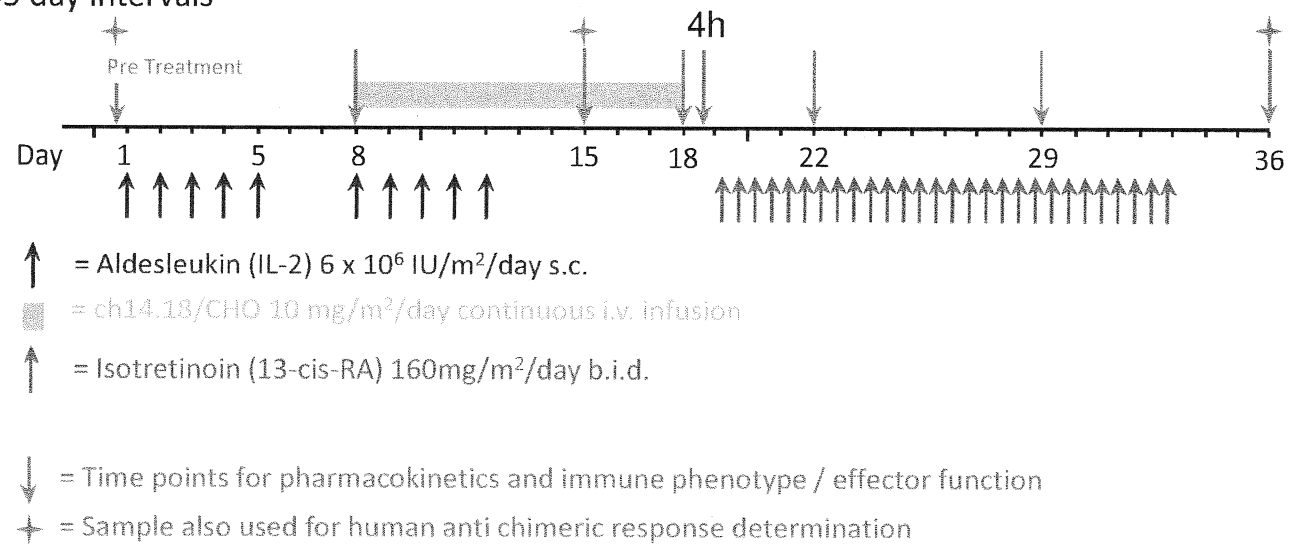
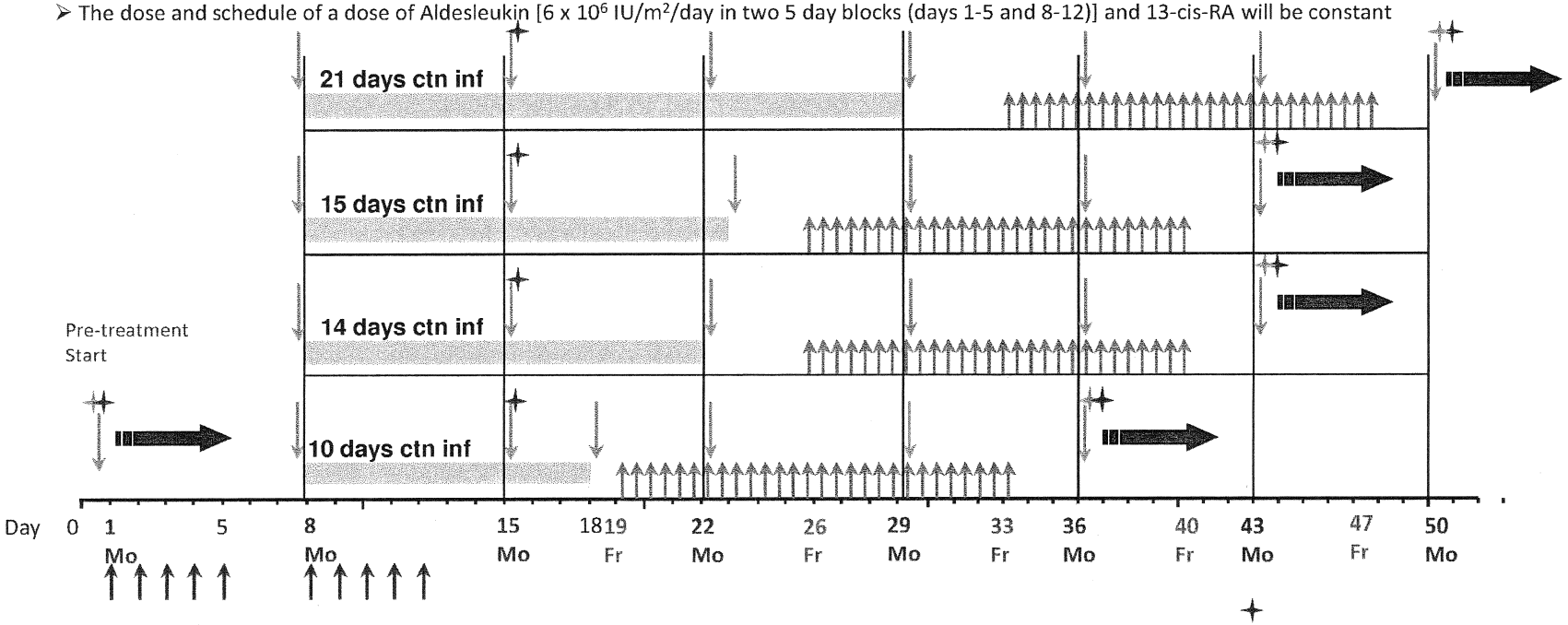


Fig. 8

Treatment Schedule

- Cycles always start on Mondays (respectively the next Monday after the last 13-cis RA dose) with Aldesleukin (IL2) s.c.
- Check time points (sampling days, start/end of ch14.18/CHO infusion as well as start /end of 13-cis RA p.o.medication) for the assigned ch14.18/CHO ctn infusion duration
- The actual dose/day (7-10-15mg/m2/day ch14.18/CHO) will be assigend by the study centre on the bases of the respective open dose level
- The dose and schedule of a dose of Aldesleukin [6 x 10^6 IU/m^2/day in two 5 day blocks (days 1-5 and 8-12)] and 13-cis-RA will be constant



= Aldesleukin (IL-2) 6 x 10^6 IU/m^2/day s.c.

= ch14.18/CHO 10 mg/m^2/day continuous i.v. infusion: start always on Mondays for advised number of days

= Isotretinoin (13-cis-RA) 160mg/m^2/day b.i.d. : start always on Fridays for 14 days

= Time points for pharmacokinetics and immune phenotype / effector function

= Sample also used for human anti chimeric response determination

= Samples for ADCC (1 Serum, 1 EDTA Plasma; day 1 (baseline), day 15)

Fig. 9

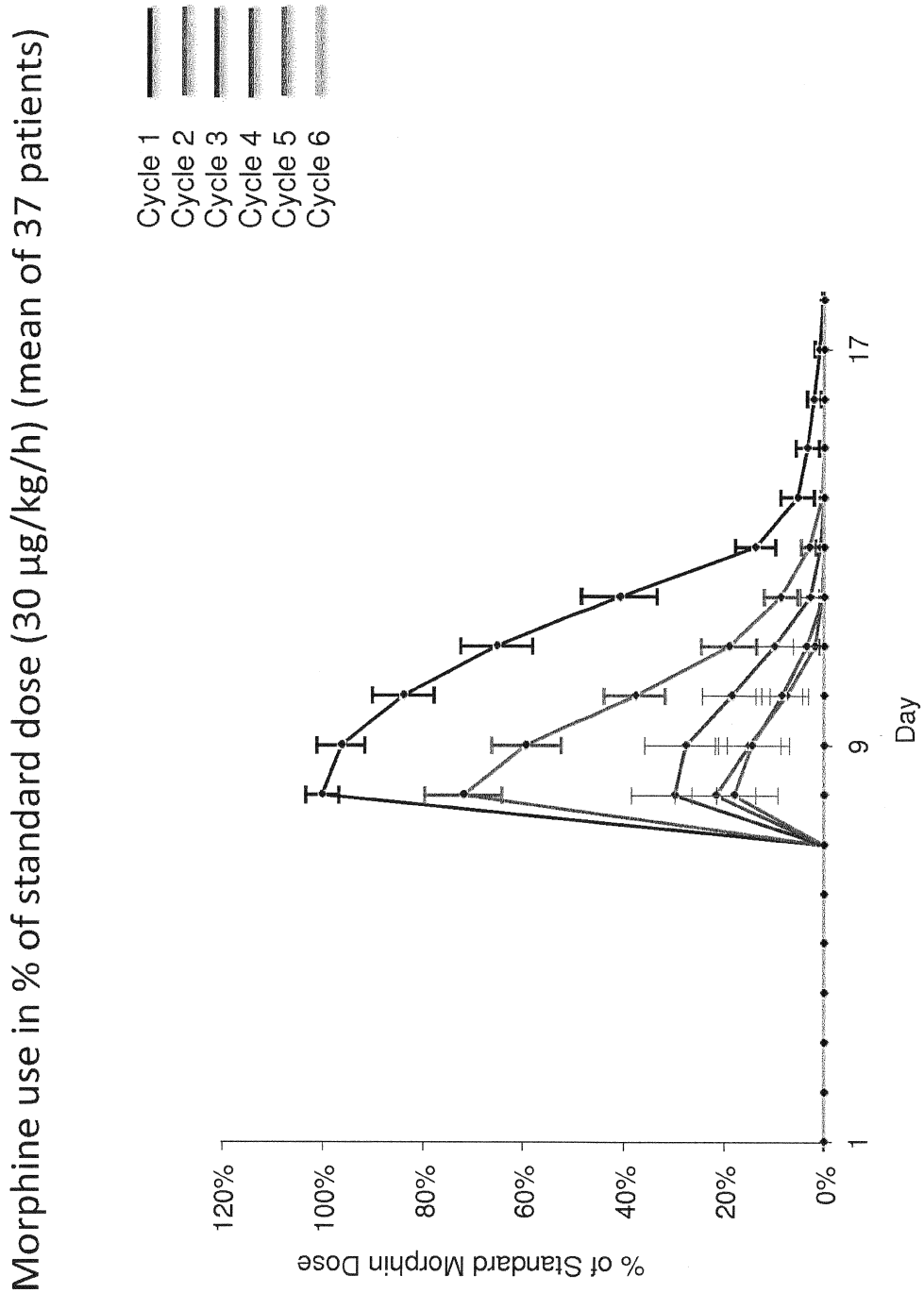

Morphine use in % of standard dose (30 µg/kg/h) (mean of 37 patients)
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
% of Standard Morphin Dose
120%
100%
80%
60%
40%
20%
0%
1
9
17
Day

Fig. 10

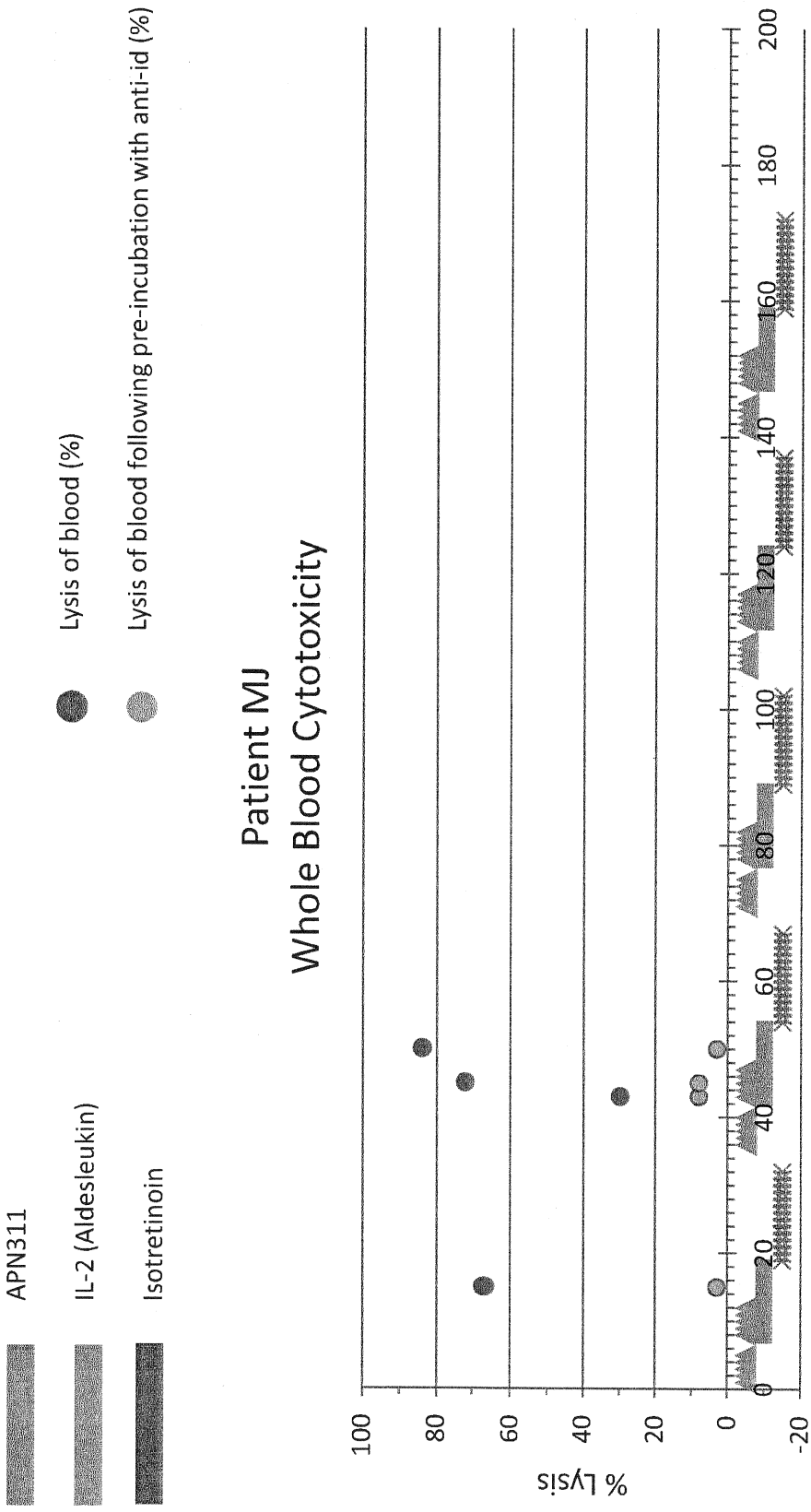

APN311
IL-2 (Aldesleukin)
Isotretinoin
Lysis of blood (%)
Lysis of blood following pre-incubation with anti-id (%)
Patient MJ
Whole Blood Cytotoxicity
% Lysis
100
80
60
40
20
0
-20
0
20
40
60
80
100
120
140
160
180
200
Treatment days

Fig. 11

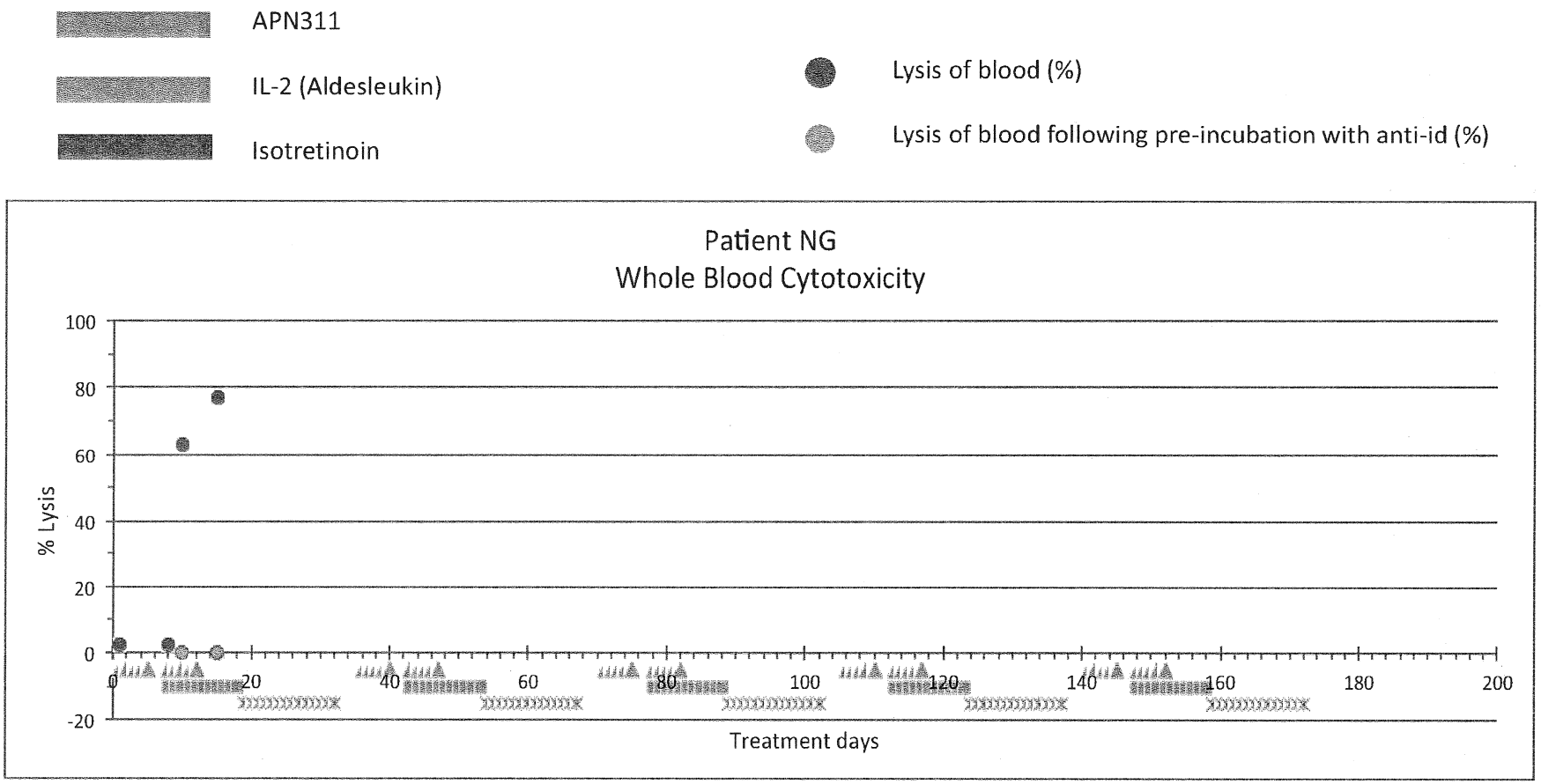

APN311
IL-2 (Aldesleukin)
Isotretinoin
Lysis of blood (%)
Lysis of blood following pre-incubation with anti-id (%)
Patient NG
Whole Blood Cytotoxicity
% Lysis
100
80
60
40
20
0
-20
0
20
40
60
80
100
120
140
160
180
200
Treatment days

Fig. 12

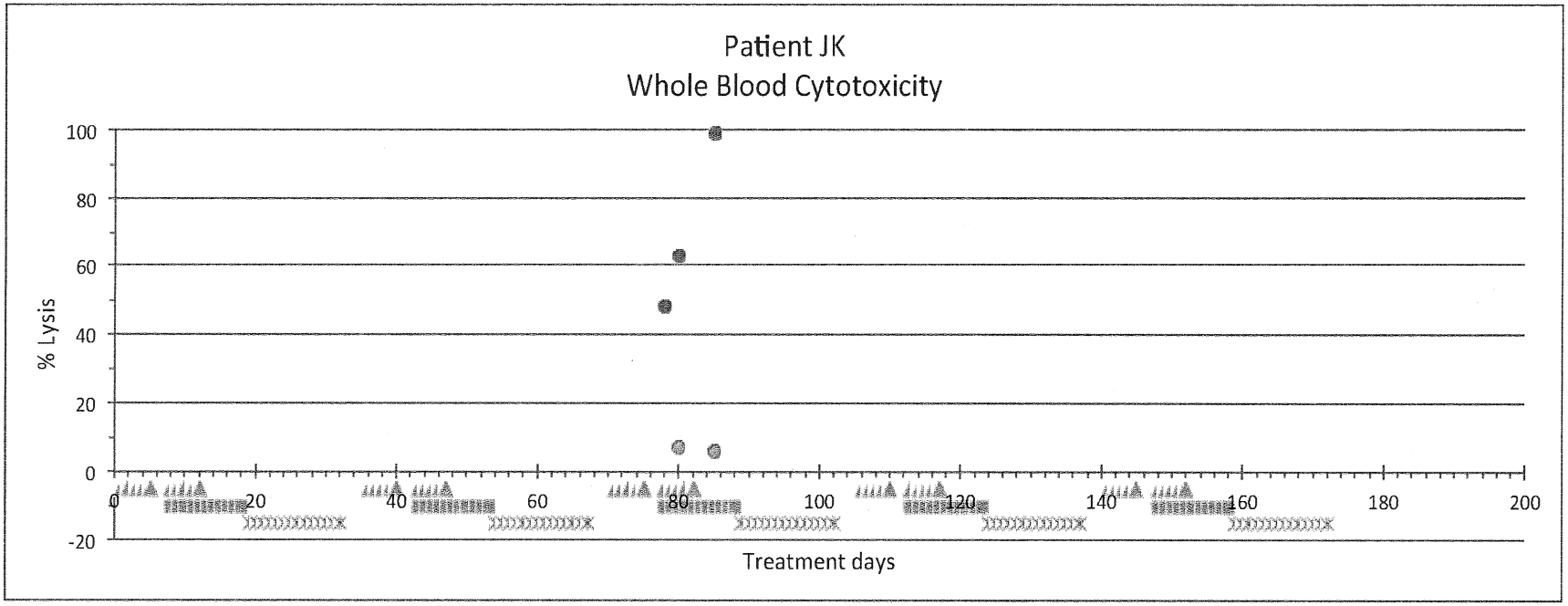

APN311
IL-2 (Aldesleukin)
Isotretinoin
Lysis of blood (%)
Lysis of blood following pre-incubation with anti-id (%)
Patient JK
Whole Blood Cytotoxicity
% Lysis
100
80
60
40
20
0
-20
0
20
40
60
80
100
120
140
160
180
200
Treatment days

Fig. 13

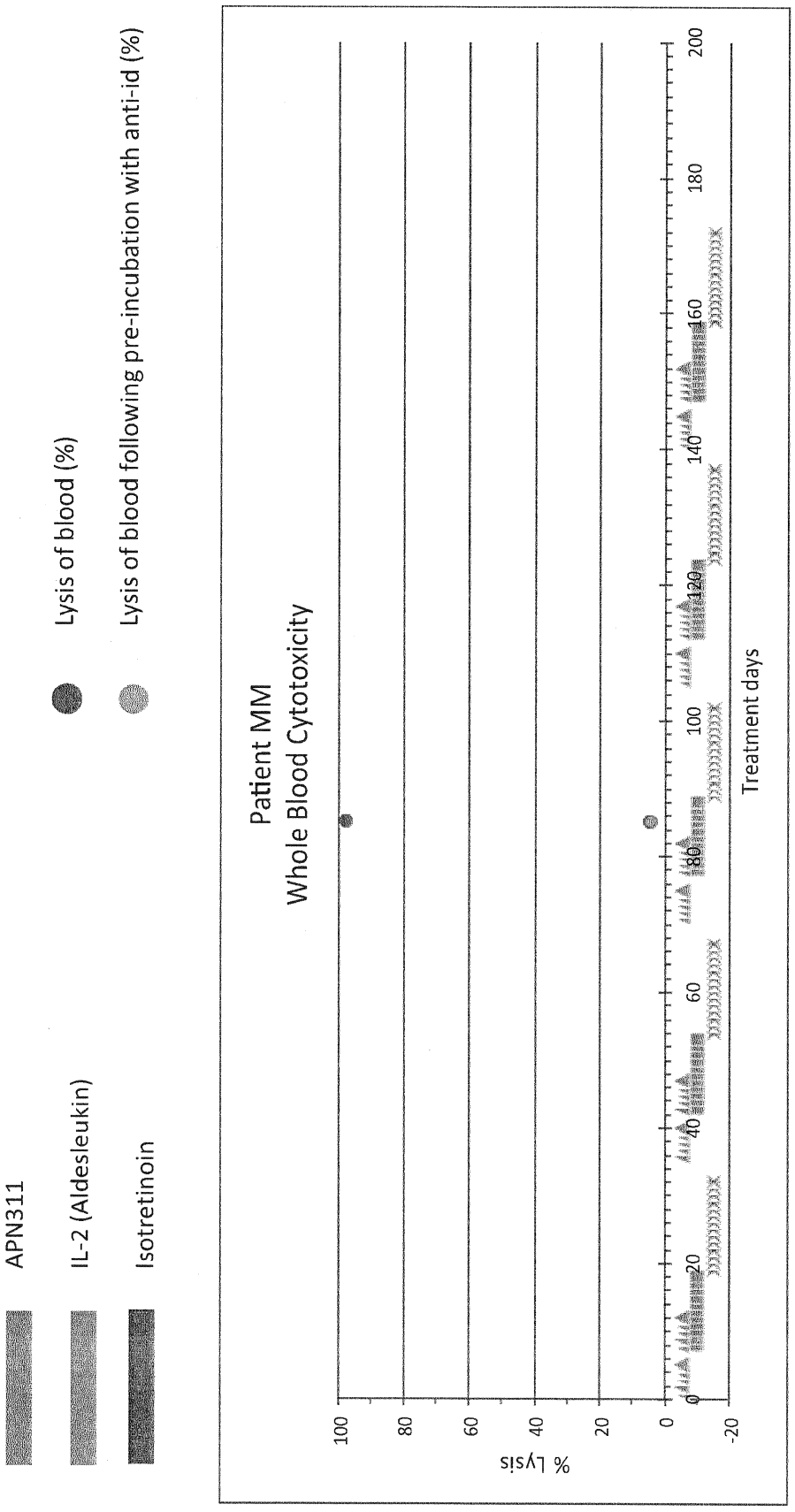

APN311
IL-2 (Aldesleukin)
Isotretinoin
Lysis of blood (%)
Lysis of blood following pre-incubation with anti-id (%)
Patient MM
Whole Blood Cytotoxicity
% Lysis
Treatment days
100
80
60
40
20
0
-20
0
20
40
60
80
100
120
140
160
180
200

Fig. 14

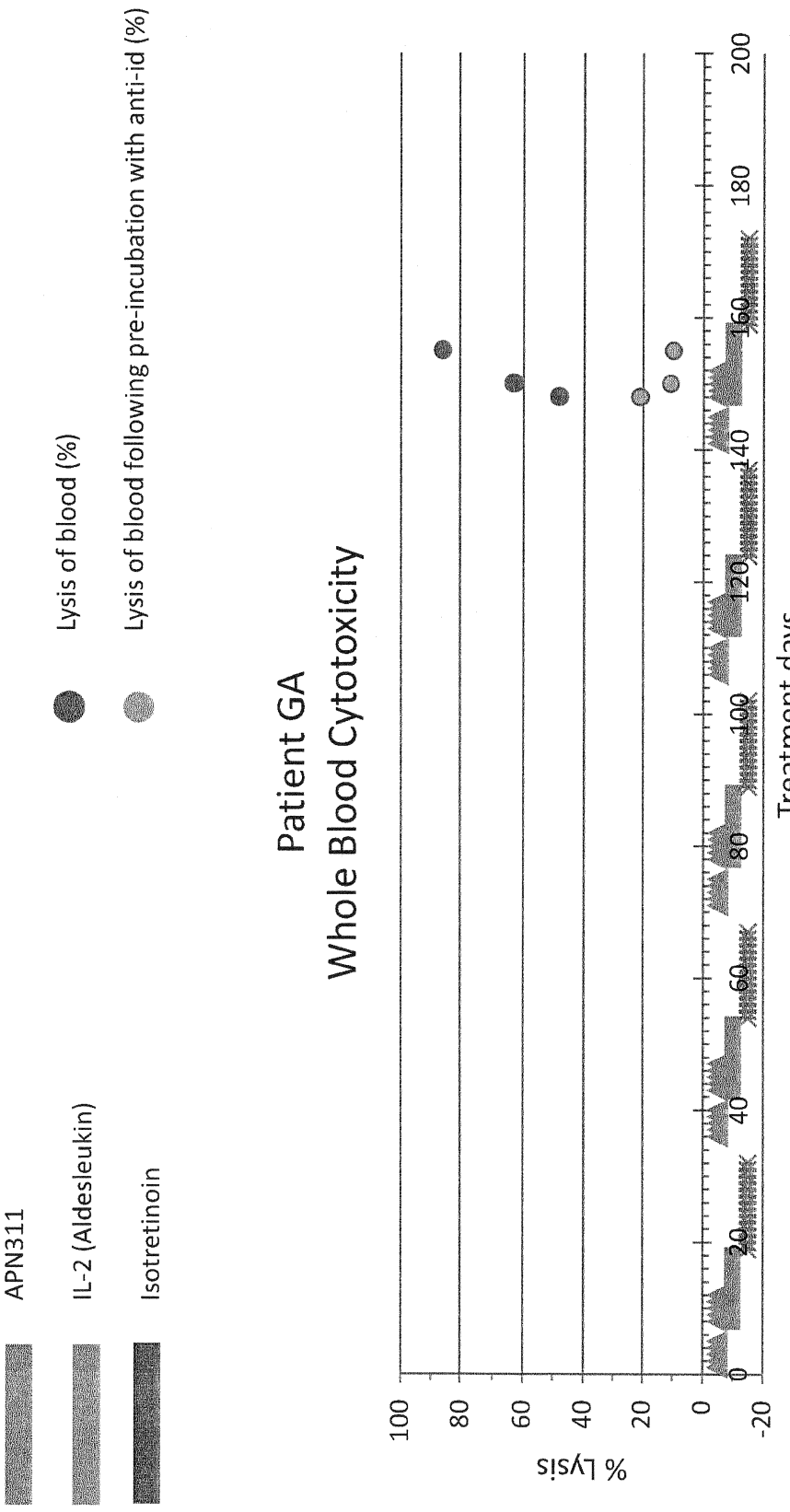

APN311
IL-2 (Aldesleukin)
Isotretinoin
Lysis of blood (%)
Lysis of blood following pre-incubation with anti-id (%)
Patient GA
Whole Blood Cytotoxicity
% Lysis
100
80
60
40
20
0
-20
0
20
40
60
80
100
120
140
160
180
200
Treatment days

Fig. 15

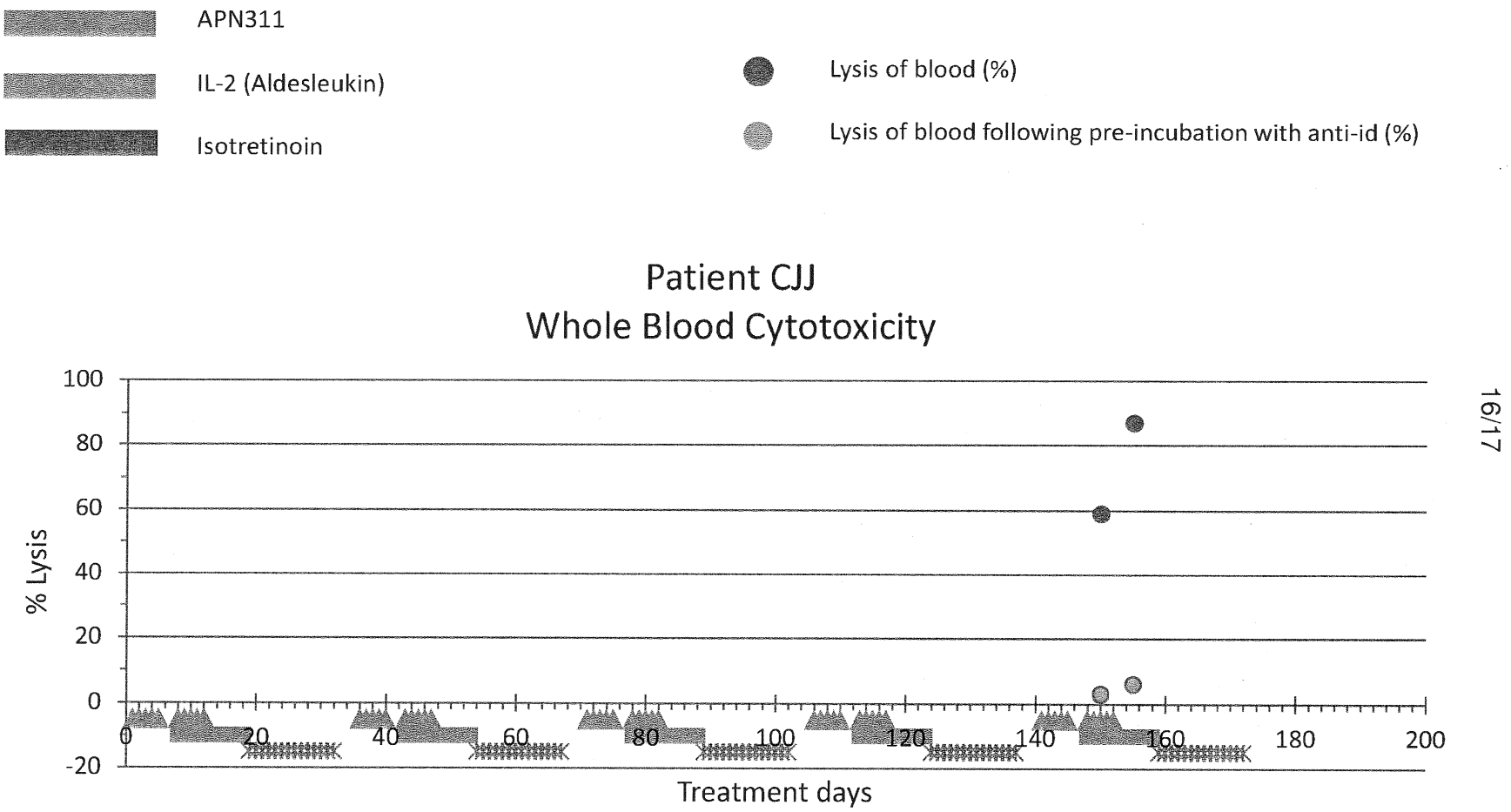

APN311
IL-2 (Aldesleukin)
Isotretinoin
Lysis of blood (%)
Lysis of blood following pre-incubation with anti-id (%)
Patient CJJ
Whole Blood Cytotoxicity
% Lysis
100
80
60
40
20
0
-20
0
20
40
60
80
100
120
140
160
180
200
Treatment days

Fig. 16

Morphine dose reduction in continuous versus non-continuous infusion

morphine application	*SIOPEN phase I trial (n = 16)*	*continuous infusion pilot (n = 37)*
starting infusion rate	50 µg/kg KG/h	30 µg/kg KG/h
additional application (bolus)	63%	14%
dose increase	50%	16%

Fig. 17