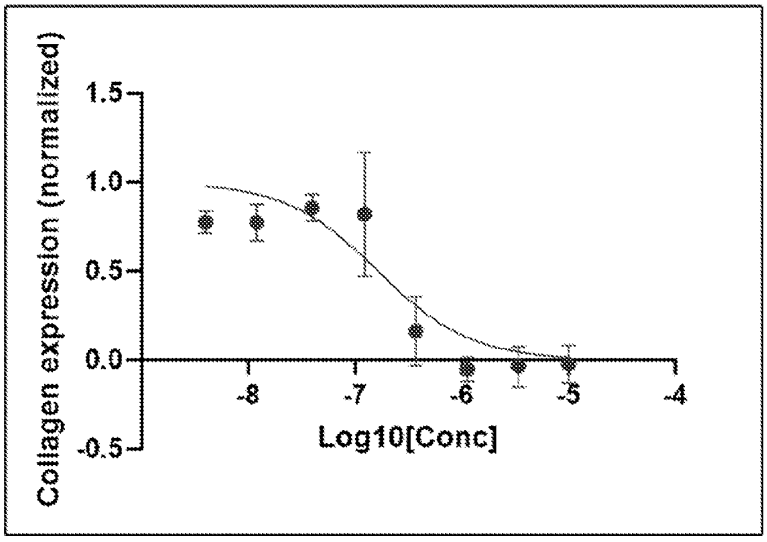

Collagen expression (normalized)
1.5
1.0
0.5
0.0
-0.5
-8
-7
-6
-5
-4
Log10[Conc]

FIGURE 1

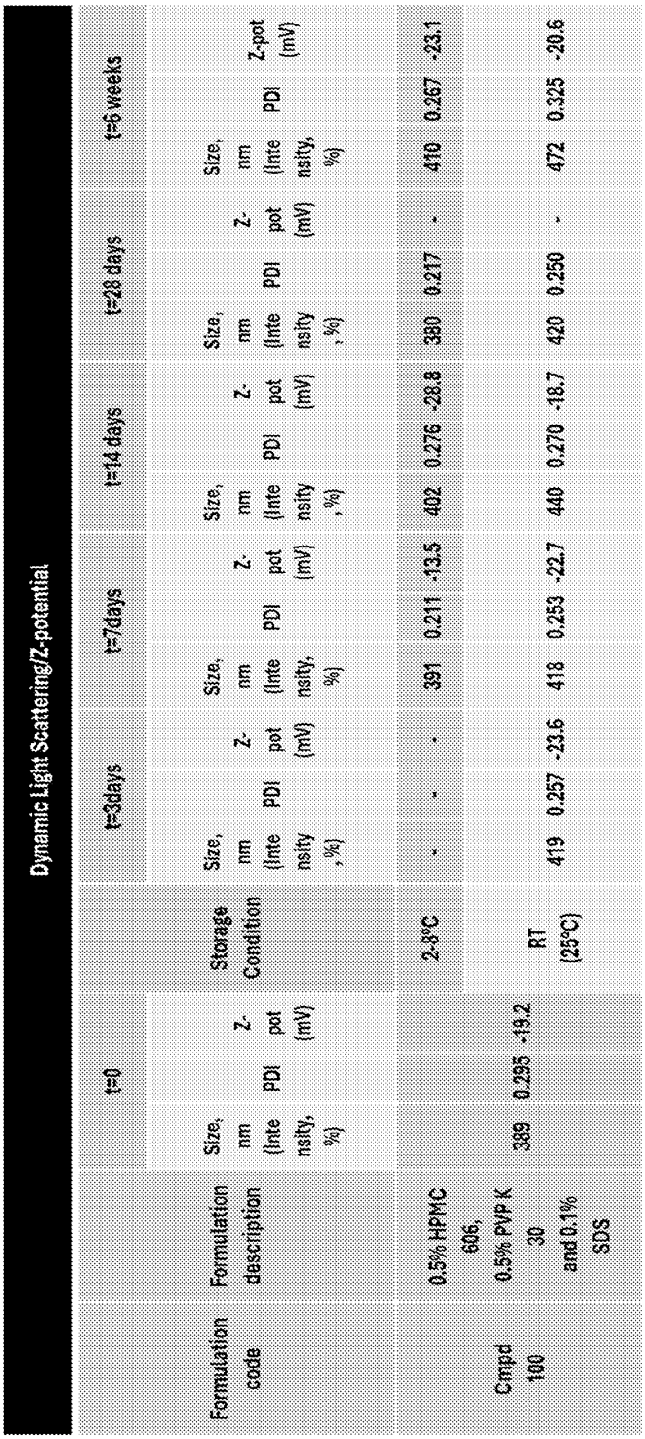
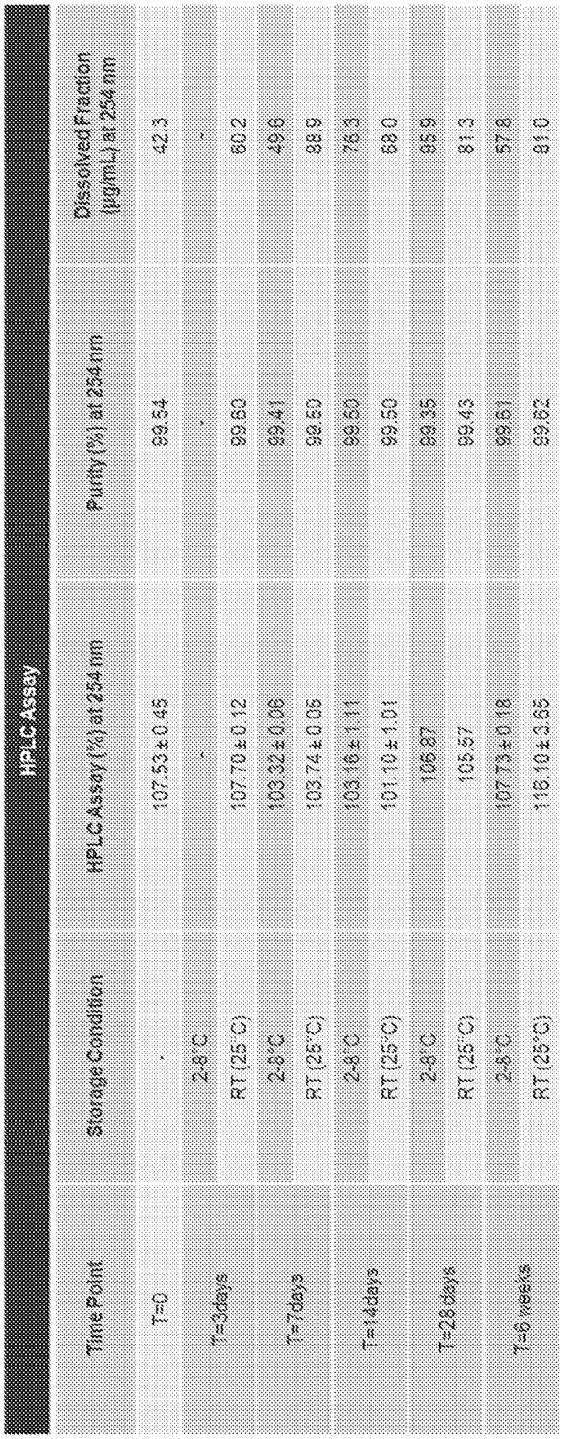

Dynamic Light Scattering/Z-potential
Formulation code
Formulation description
t=0
Size, nm (Intensity, %)
PDI
Z-pot (mV)
Storage Condition
t=3days
t=7days
t=14 days
t=28 days
t=6 weeks
Cmpd 100
0.5% HPMC 606, 0.5% PVP K 30 and 0.1% SDS
389
0.293
-19.2
2-8°C
RT (25°C)
419
0.257
-23.6
391
0.211
-13.5
402
0.276
-28.8
380
0.217
-
410
0.267
-23.1
418
0.253
-22.7
440
0.270
-18.7
420
0.250
-
472
0.325
-20.6

FIGURE 2



HPLC Assay				
Time Point	Storage Condition	HPLC Assay (%) at 254 nm	Purity (%) at 254 nm	Dissolved Fraction (µg/mL) at 254 nm
T=0	-	107.53 ± 0.45	99.54	42.3
T=3days	2-8°C	-	-	-
	RT (25°C)	107.70 ± 0.12	99.60	60.2
T=7days	2-8°C	103.32 ± 0.06	99.41	49.6
	RT (25°C)	103.74 ± 0.05	99.50	88.9
T=14days	2-8°C	103.16 ± 1.11	99.50	76.3
	RT (25°C)	101.10 ± 1.01	99.50	68.0
T=28 days	2-8°C	106.87	99.35	85.9
	RT (25°C)	105.57	99.43	81.3
T=6 weeks	2-8°C	107.73 ± 0.18	99.61	57.8
	RT (25°C)	118.10 ± 3.65	99.62	81.0

FIGURE 3

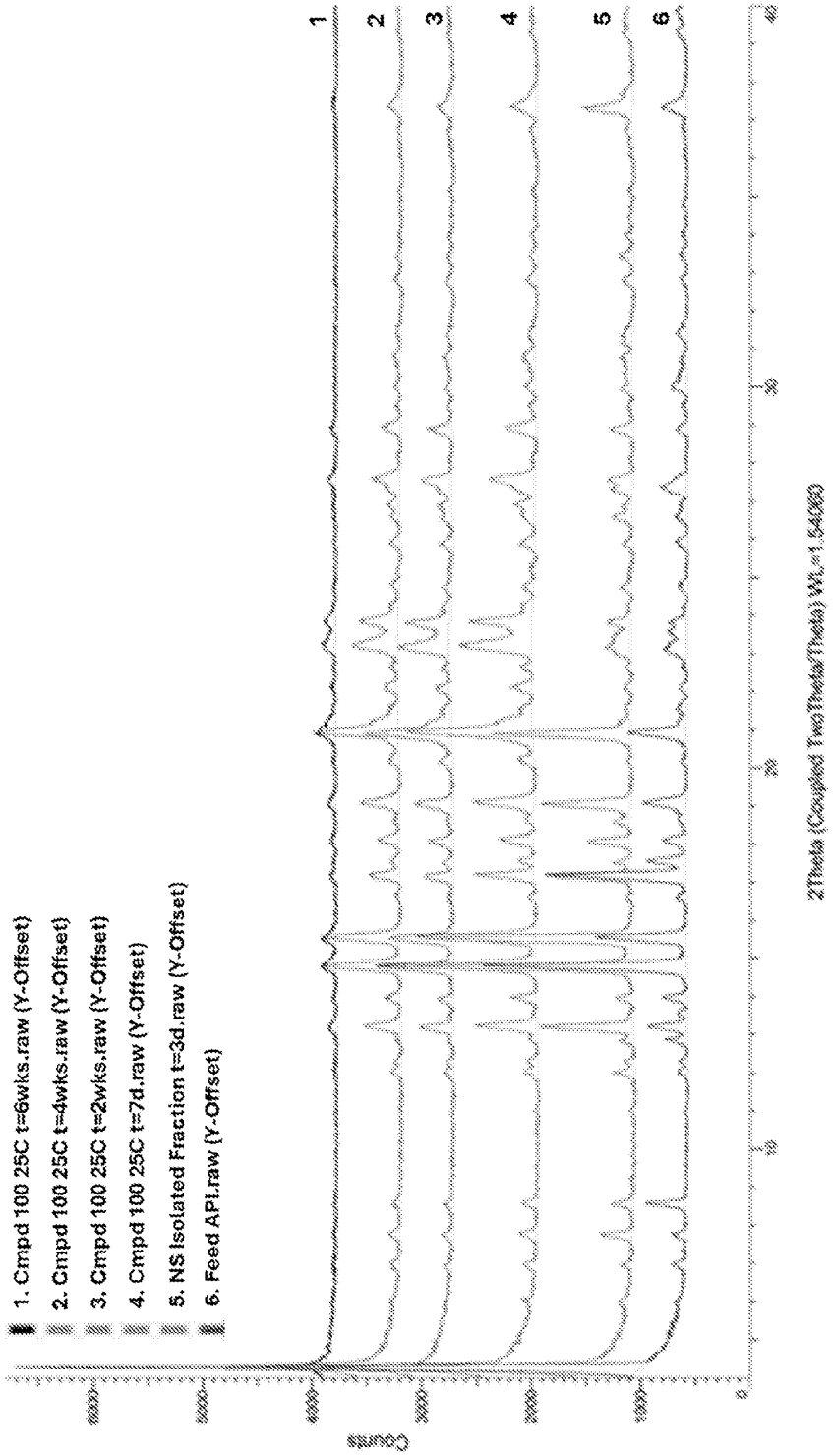

1. Cmpd 100 25C t=6wks.raw (Y-Offset)
2. Cmpd 100 25C t=4wks.raw (Y-Offset)
3. Cmpd 100 25C t=2wks.raw (Y-Offset)
4. Cmpd 100 25C t=7d.raw (Y-Offset)
5. NS Isolated Fraction t=3d.raw (Y-Offset)
6. Feed API.raw (Y-Offset)
Counts
2Theta (Coupled TwoTheta/Theta) WL=1.54060
1
2
3
4
5
6

FIGURE 4A

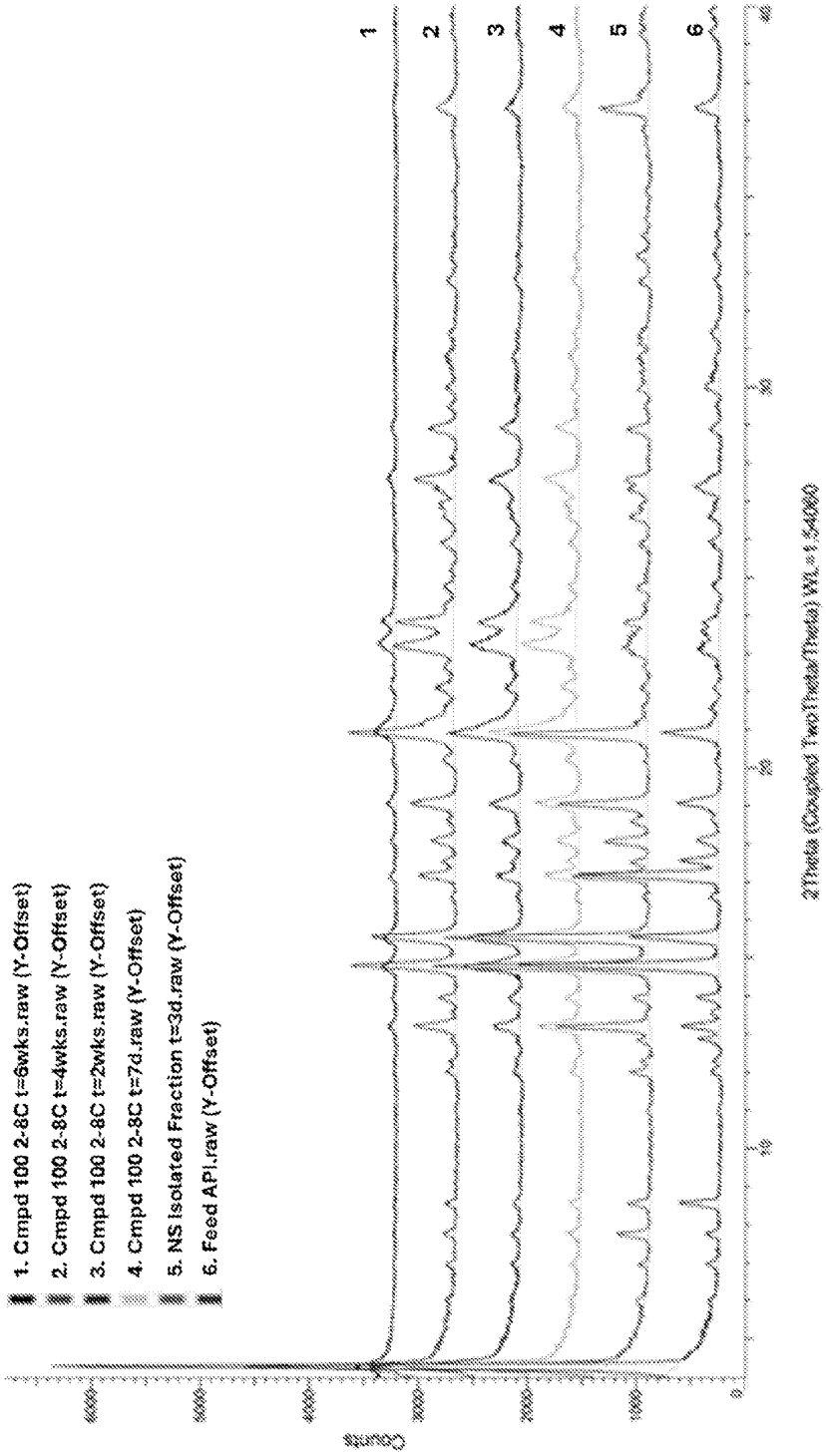

1. Cmpd 100 2-8C t=6wks.raw (Y-Offset)
2. Cmpd 100 2-8C t=4wks.raw (Y-Offset)
3. Cmpd 100 2-8C t=2wks.raw (Y-Offset)
4. Cmpd 100 2-8C t=7d.raw (Y-Offset)
5. NS Isolated Fraction t=3d.raw (Y-Offset)
6. Feed API.raw (Y-Offset)
1
2
3
4
5
6
Lin (Counts)
6000
5000
4000
3000
2000
1000
0
10
20
30
40
2Theta (Coupled Two Theta/Theta) WL=1.54060

FIGURE 4B

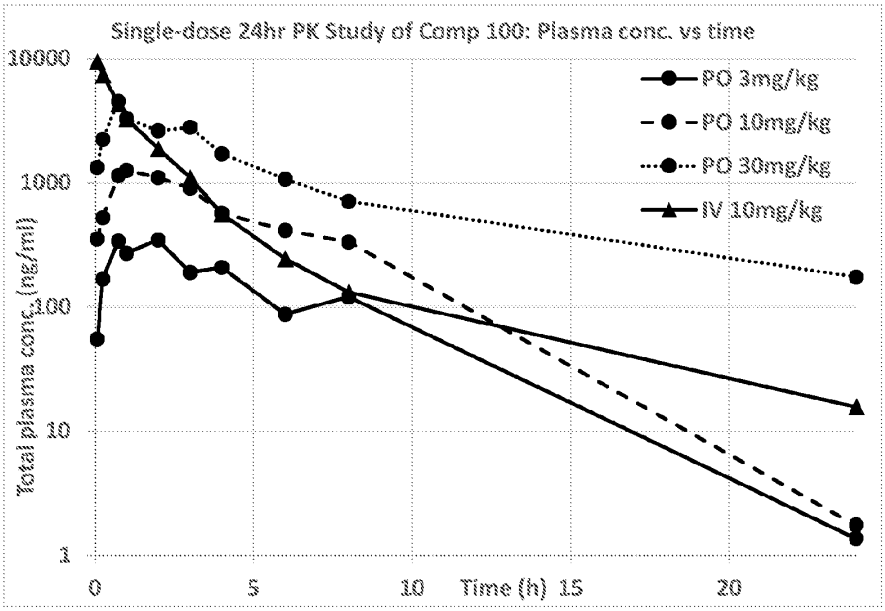

Single-dose 24hr PK Study of Comp 100: Plasma conc. vs time
10000
1000
100
10
1
Total plasma conc. (ng/ml)
0
5
10
Time (h)
15
20
PO 3mg/kg
PO 10mg/kg
PO 30mg/kg
IV 10mg/kg

FIGURE 5

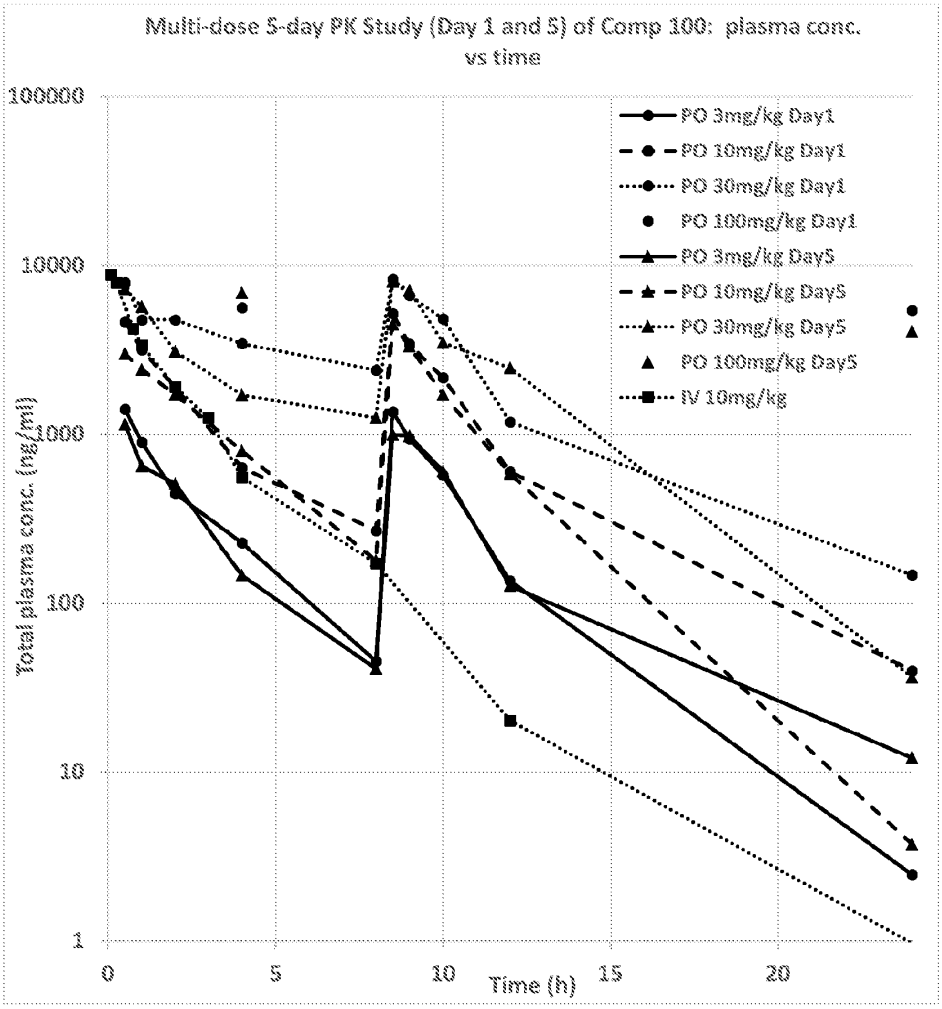

Multi-dose 5-day PK Study (Day 1 and 5) of Comp 100: plasma conc. vs time
Total plasma conc. (ng/ml)
100000
10000
1000
100
10
1
0
5
10
15
20
Time (h)
PO 3mg/kg Day1
PO 10mg/kg Day1
PO 30mg/kg Day1
PO 100mg/kg Day1
PO 3mg/kg Day5
PO 10mg/kg Day5
PO 30mg/kg Day5
PO 100mg/kg Day5
IV 10mg/kg

FIGURE 6

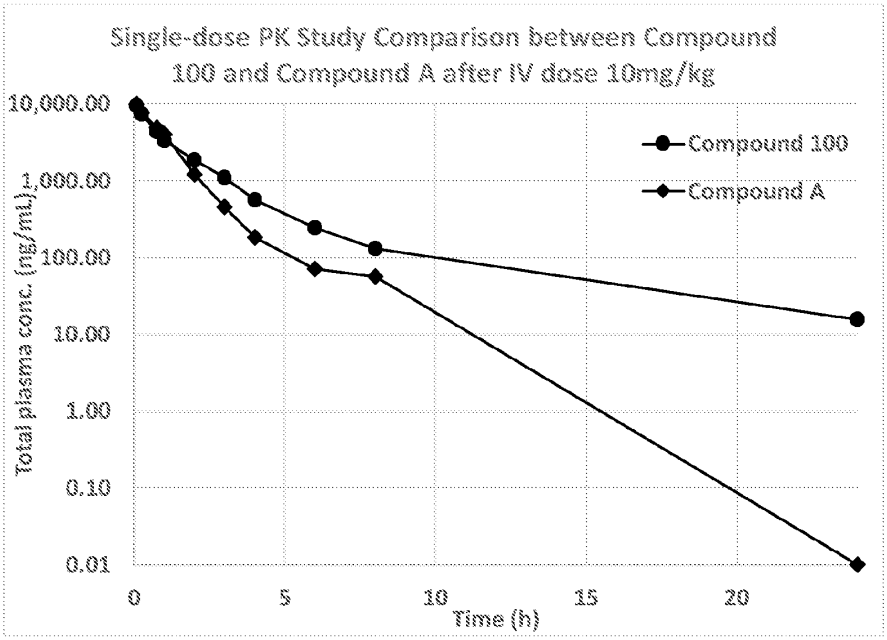


FIGURE 7

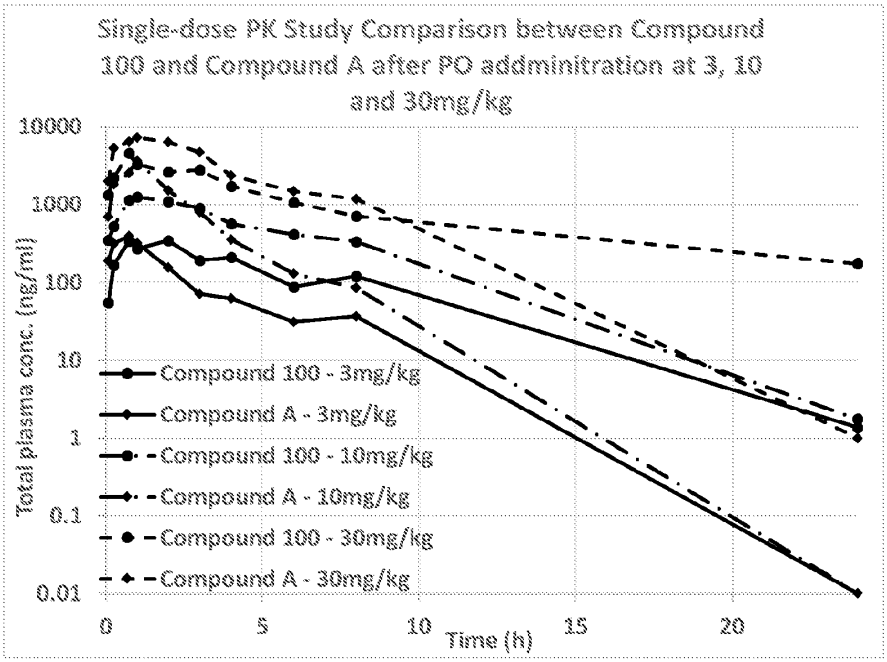


FIGURE 8

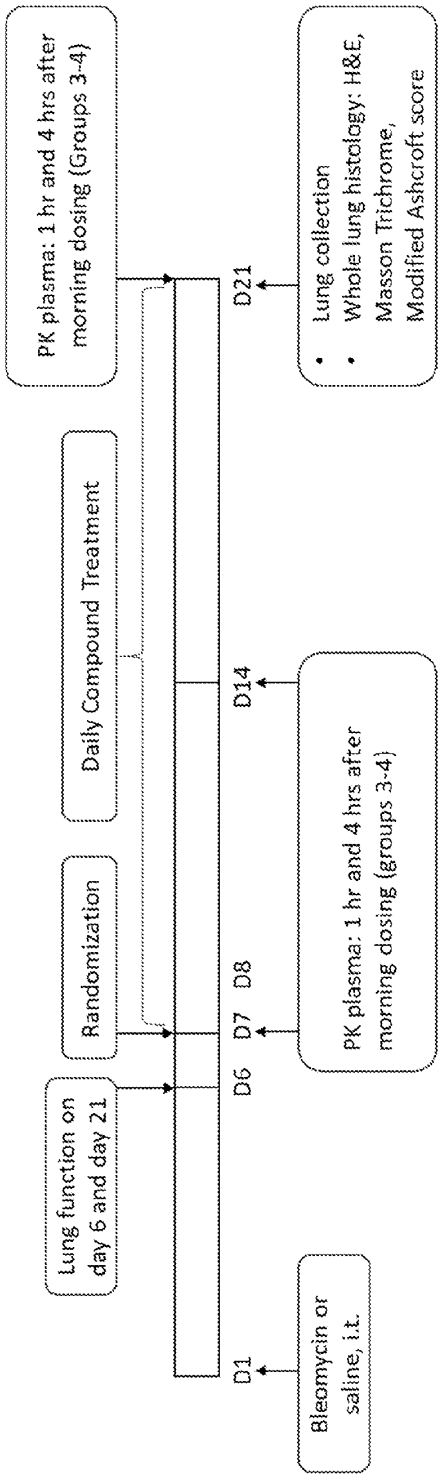

PK plasma: 1 hr and 4 hrs after morning dosing (Groups 3-4)
Daily Compound Treatment
Randomization
Lung function on day 6 and day 21
Bleomycin or saline, i.t.
D1
D6
D7
D8
D14
D21
PK plasma: 1 hr and 4 hrs after morning dosing (groups 3-4)
Lung collection
Whole lung histology: H&E, Masson Trichrome, Modified Ashcroft score

FIGURE 9

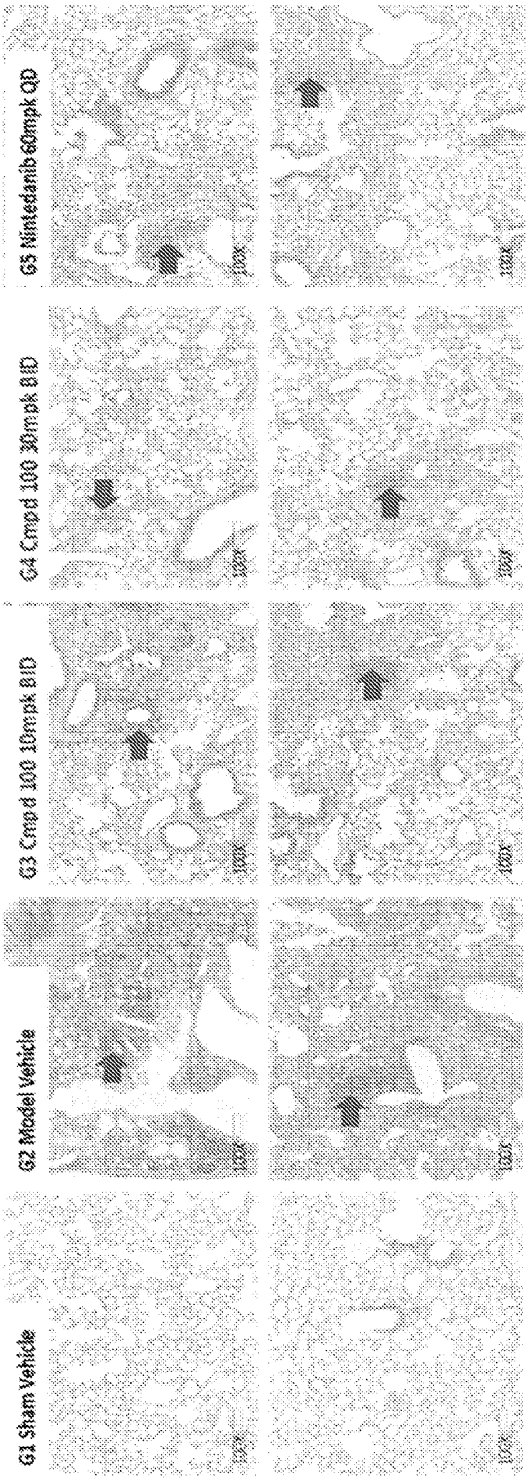

G1 Sham Vehicle
G2 Model Vehicle
G3 Cmpd 100 10mpk BID
G4 Cmpd 100 30mpk BID
G5 Nintedanib 60mpk QD
100X
100X
100X
100X
100X
100X
100X
100X
100X
100X

FIGURE 10

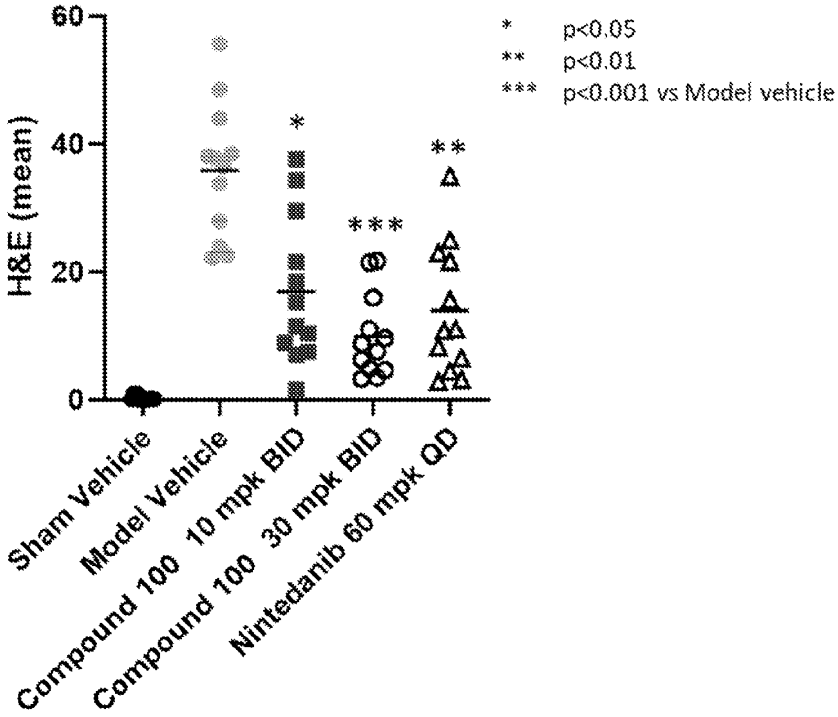

60
40
20
0
H&E (mean)
*
**
***
* p<0.05
** p<0.01
*** p<0.001 vs Model vehicle
Sham Vehicle
Model Vehicle
Compound 100 10 mpk BID
Compound 100 30 mpk BID
Nintedanib 60 mpk QD

FIGURE 11

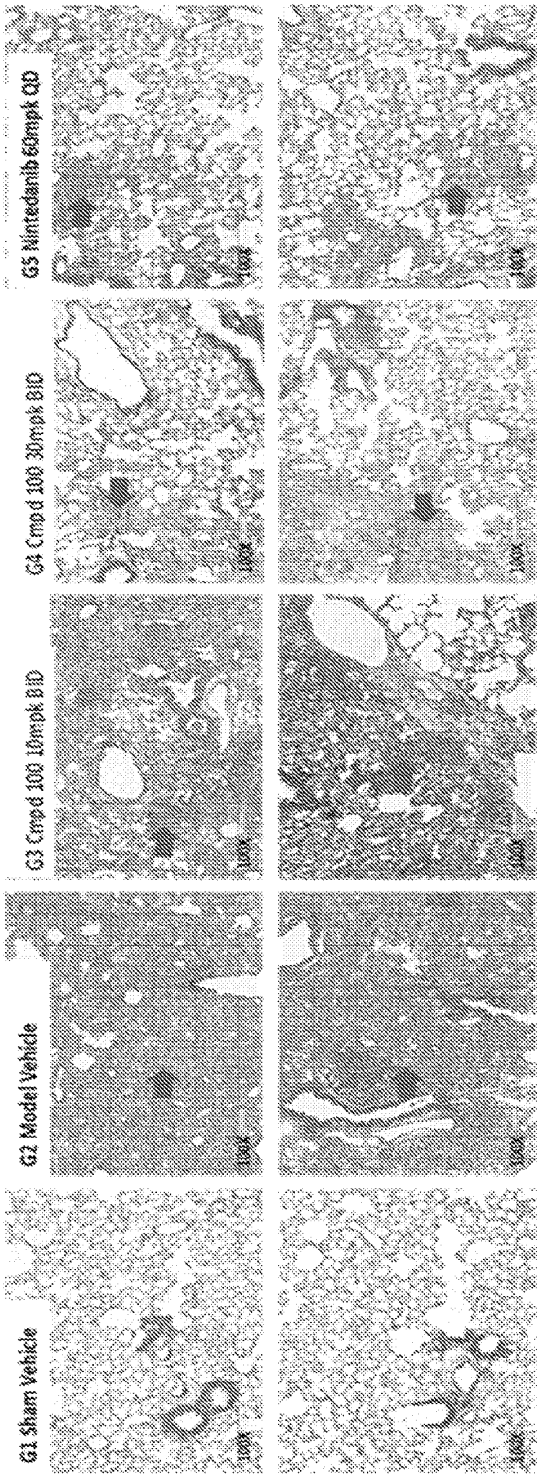

G1 Sham Vehicle
G2 Model Vehicle
G3 Cmpd 100 10mpk BID
G4 Cmpd 100 30mpk BID
G5 Nintedanib 60mpk QD
100X
100X
100X
100X
100X
100X
100X
100X
100X
100X

FIGURE 12

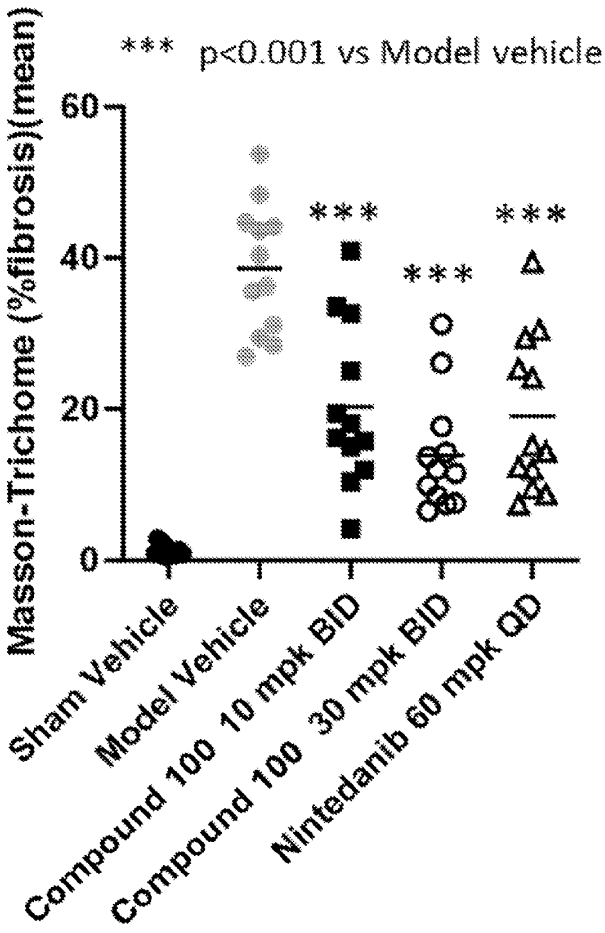

*** p<0.001 vs Model vehicle
Masson-Trichome (%fibrosis)(mean)
60
40
20
0
***
***
***
Sham Vehicle
Model Vehicle
Compound 100 10 mpk BID
Compound 100 30 mpk BID
Nintedanib 60 mpk QD

FIGURE 13

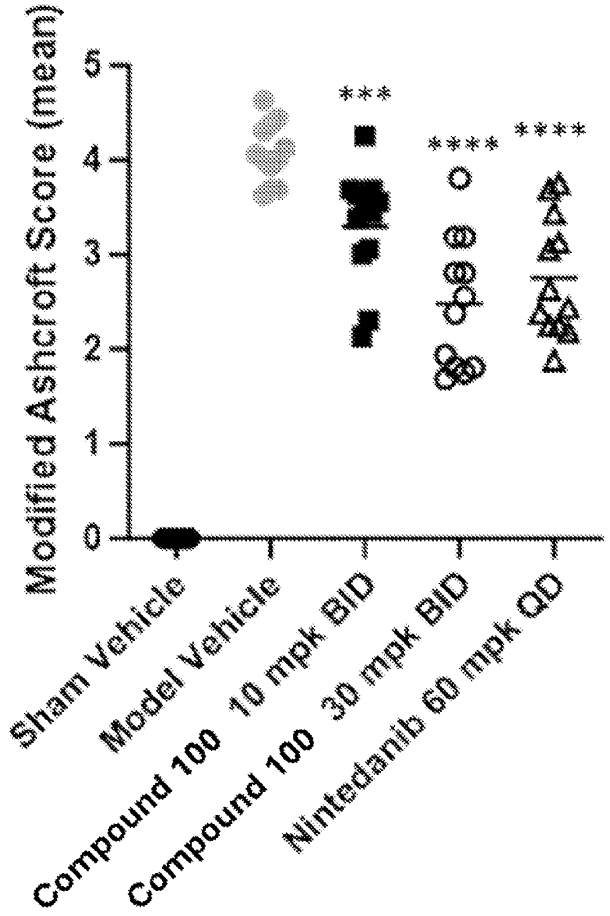

Modified Ashcroft Score (mean)
0
1
2
3
4
5
***
****
****
Sham Vehicle
Model Vehicle
10 mpk BID
Compound 100
30 mpk BID
Compound 100
Nintedanib 60 mpk QD

FIGURE 14

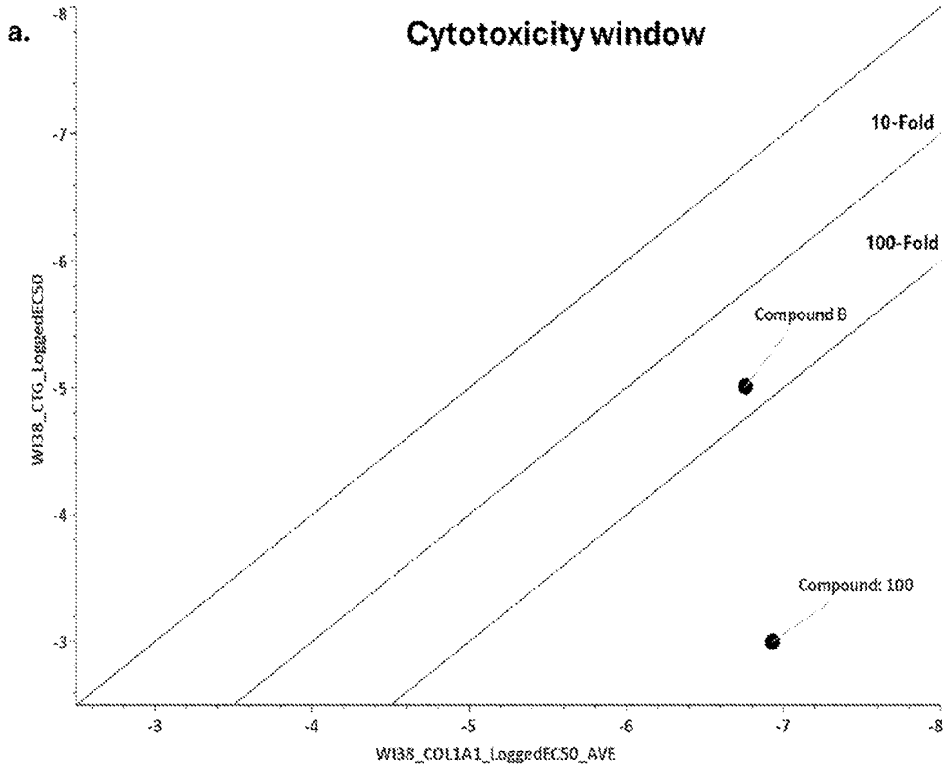

a.
Cytotoxicity window
10-Fold
100-Fold
Compound 8
Compound: 100
WI38_CTG_LoggedEC50
WI38_COL1A1_LoggedEC50_AVE
-3
-4
-5
-6
-7
-8

FIGURE 15

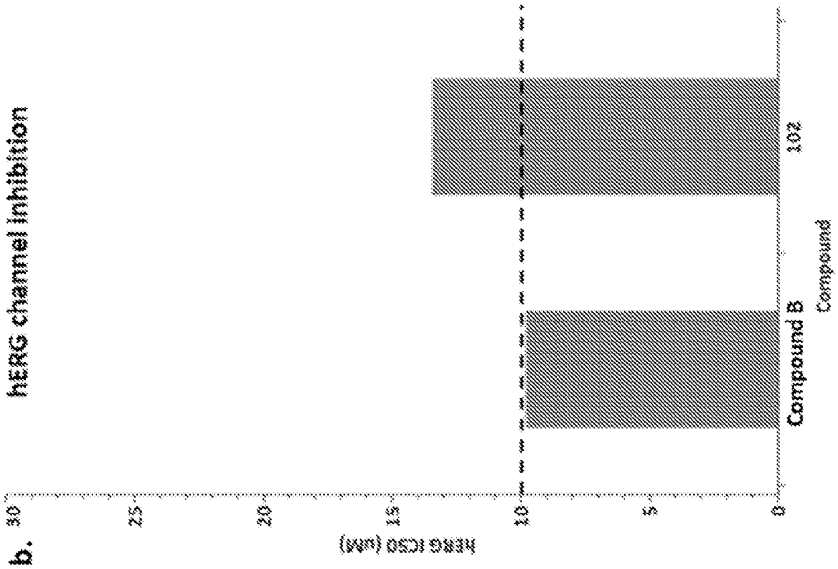


FIGURE 16B

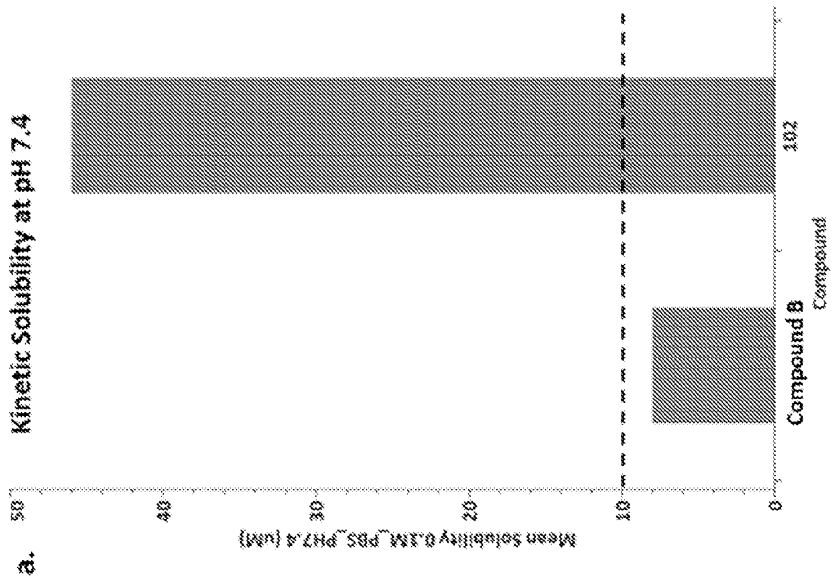


FIGURE 16A