

Figures

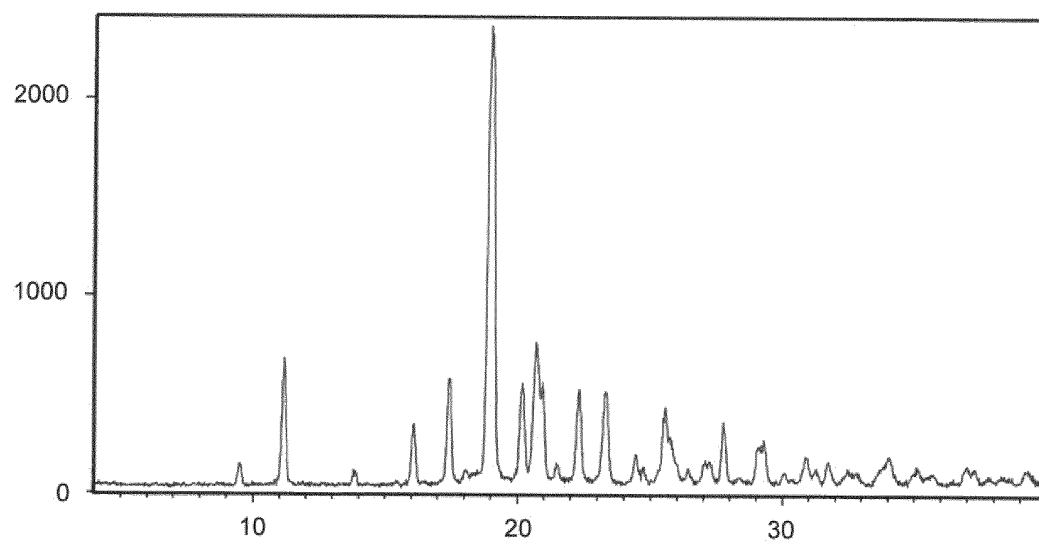


Fig. 1

2/17

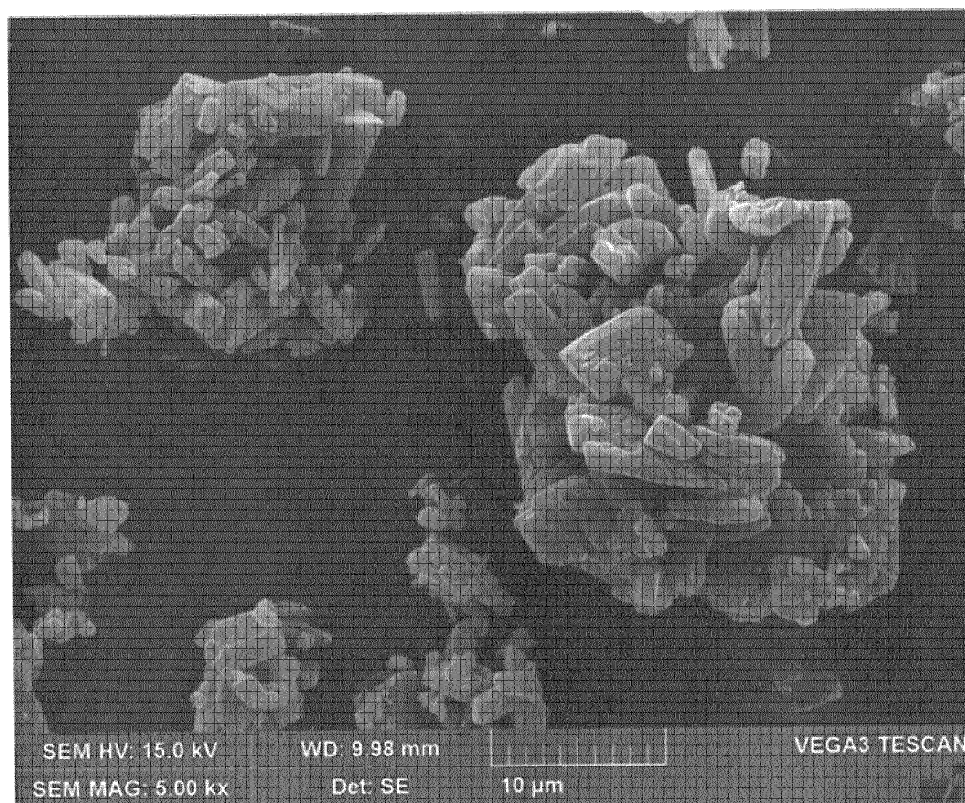


Fig. 2

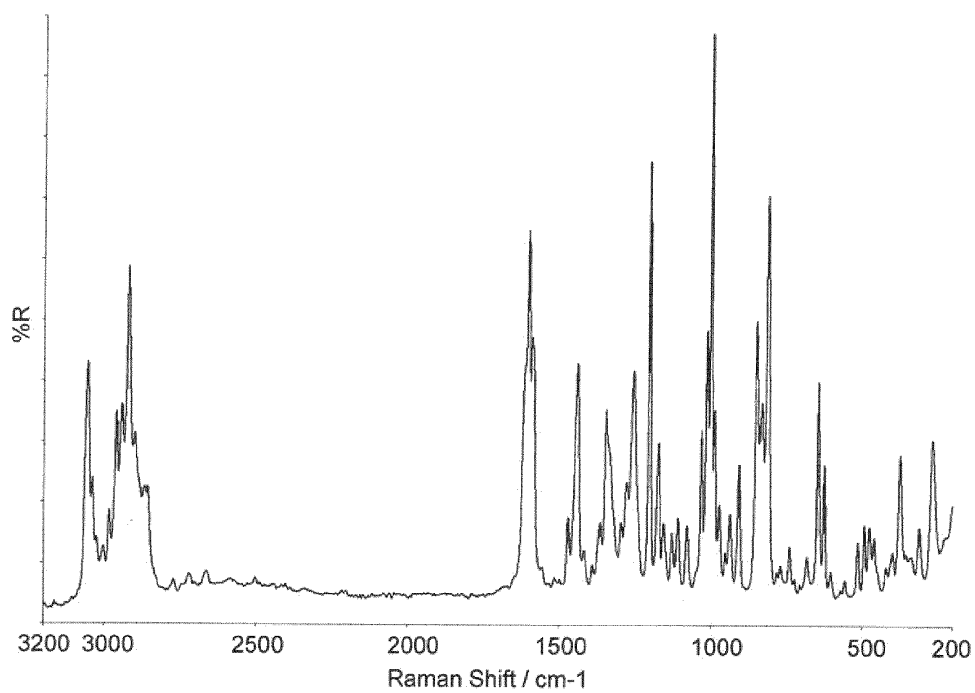


Fig. 3

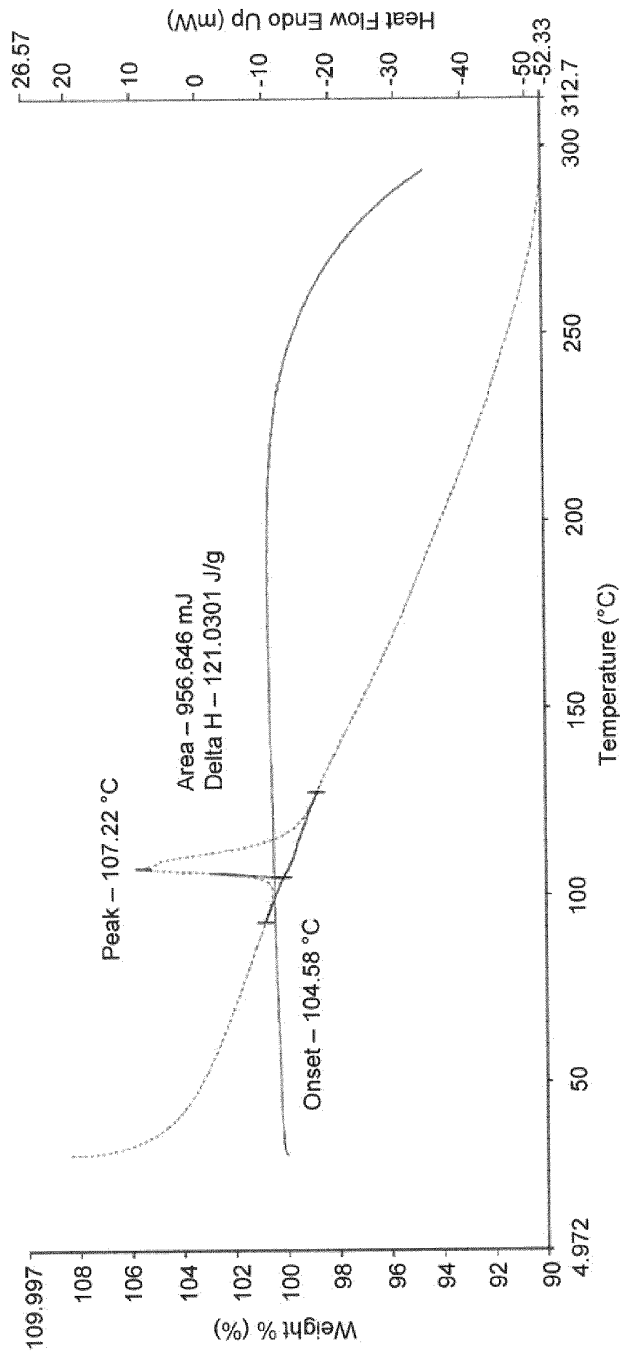
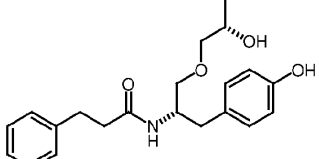


Fig. 4

Analytical Data Sheet

Product Code	NRD135 S E1 Form 1
Batch No.	RM1407-269 (141232)-M
Batch Quantity	1.7 kg (2014 Regis, Micron)
Storage Conditions	Store below 25°C
Shipping Conditions	Ship below 30°C
Retest Date	August 2019
Restriction	not for human use
Structure:	 NRD135 S E1 C₂₁H₂₇NO₄ Mol. Wt.: 357,44

Analytical Data

Attribute	Method	Result
Appearance	visual	white powder*
Assay	HPLC	98.1%*
Identity	NMR	conforms to structure*
	DSC	conforms to Form 1**
PSD	Laser Diffraction	D ₉₀ 3 µm*** D ₁₀₀ 9 µm***

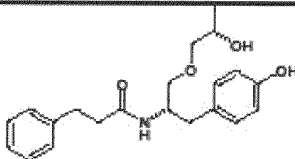
*based on Regis CoA dated 14-Dec-2017based on data obtained by Solid Chem

**based on Pharmaterial/Quotient Results

***based on Micron results (I 5 2nd pass)

Fig. 5

 NOVAREMED	Analytical Data Sheet
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Product Code	NRD135 S E1 Form 2
Batch No.	COEN 4-091-M
Batch Quantity	80 g
Storage Conditions	Store below 25°C
Shipping Conditions	Ship below 30°C
Retest Date	August 2019
Restriction	not for human use
Structure:	 NRD135 S E1 C₂₁H₂₇NO₄ Mol. Wt.: 357,44

Analytical Data

Attribute	Method	Result
Appearance	visual	white powder*
Assay (Potency)	HPLC	98.7%**
Identity	NMR	conforms to structure**
	DSC	conforms to Form 2***
PSD	Laser Diffraction	D90 10 µm* D100 19 µm*

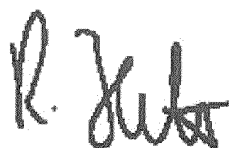
* based on data obtained from MCKO

** based on tests performed on the unmicronised material AR-115956 DRL

***based on data obtained by Solid Chem

Basel, Date

30. Jul 2018



Robert Hett QA consultant for Novaremed

Fig. 6

7/17

Week	Sequence – Period Treatment	Material Batch ID	Dose Route	Target Dose Level (mg/kg)	Animal ID	Animal Bodyweight (kg)	Weight of Dose Administered (g)	Calculated Dose Concentration (mg/mL) ^A	Calculated 'mg' Received (mg) ^B	Calculated Dose Level (mg/kg) ^B	% Difference from Target
1	1-1 Old	141232	PO	60	001M	11.5	58.4	12.0	701	61.0	1.6
					002M	10.6	54.2	12.0	651	61.4	2.3
					003M	11.4	57.8	12.0	693	60.6	1.0
	2-1 New	COEN4_091-M	PO	60	004M	11.0	54.9	12.3	675	61.6	2.7
					005M	10.6	53.4	12.3	657	62.0	3.3
					006M	9.59	48.5	12.3	596	62.2	3.6
2	1-2 New	COEN4-091-M	PO	60	001M	11.5	56.9	12.8	728	63.5	5.8
					002M	10.9	53.9	12.8	689	63.4	5.6
					003M	11.4	56.6	12.8	724	63.8	6.3
	2-2 Old	141232	PO	60	004M	10.9	53.4	12.3	656	60.3	0.5
					005M	10.2	51.8	12.3	637	62.4	4.0
					006M	9.54	47.3	12.3	582	61.0	1.7

Fig. 7

8/17

Week	Sequence – Period Treatment	Material Batch ID	Dose Route	Target Dose Level (mg/kg)	Animal ID	Target Blood Sampling Times (minutes after dosing)									
						15	30	60	120	180	240	360	480	720	1500
						Actual Blood Sampling Times (minutes after dosing)									
1	1-1 Old	141232	PO	60	001M	16	30	60	120	180	240	360	474	720	1500
					002M	16	30	60	120	180	240	360	474	720	1500
					003M	16	30	60	120	180	240	360	475	720	1500
	2-1 New	COEN4_091-M	PO	60	004M	16	30	60	120	180	241	360	475	720	1500
					005M	16	30	60	120	180	241	360	475	720	1500
					006M	15	30	60	120	180	241	360	475	720	1500
2	1-2 New	COEN4-091-M	PO	60	001M	15	30	60	120	180	240	360	480	720	1504
					002M	15	30	60	120	180	240	360	480	720	1504
					003M	15	30	60	121	180	240	360	480	720	1504
	2-2 Old	141232	PO	60	004M	15	30	60	122	180	240	361	480	720	1504
					005M	15	30	60	122	180	240	361	480	720	1504
					006M	15	30	60	122	180	240	361	480	720	1504

Fig. 8

9/17

Week	Sequence – Period Treatment	Material Batch ID	Dose Route	Target Dose Level (mg/kg)	Animal ID	Concentration of NRD135S.E1 in dog plasma (ng/mL)										
						Timepoint (h)										
						0	0.25	0.5	1	2	3	4	6	8	12	24
1	1-1 Old	141232	PO	60	001M	<LLOQ	4527	3857	1893	557	306	198	276	369	215	54.6
					002M	<LLOQ	8012	5944	4288	1209	799	663	660	805	831	61.3
					003M	<LLOQ	5458	4378	3753	1286	806	560	778	550	532	67.4
	Mean					<LLOQ	5999	4726	3311	1017	637	474	572	575	526	61.1
	SD					NA	1804	1086	1257	401	287	244	263	219	308	6.43
	2-1 New	COEN4_091-M	PO	60	004M	<LLOQ	3250	10110	5813	1065	463	335	647	635	337	56.4
					005M	<LLOQ	9680	7690	3392	1180	462	436	347	463	748	160
					006M	<LLOQ	8938	7459	4424	673	239	205	694	567	371	30.3
	Mean					<LLOQ	7289	8419	4543	973	388	325	563	555	485	82.3
	SD					NA	3518	1469	1215	266	129	116	188	86.6	228	68.7
2	1-2 New	COEN4-091-M	PO	60	001M	<LLOQ	13817	9588	3511	618	264	284	448	422	342	24.4
					002M	<LLOQ	15044	11333	7578	1690	518	416	784	1028	1173	94.4
					003M	<LLOQ	12771	13336	7486	1698	541	329	459	614	635	137
	Mean					<LLOQ	13877	11419	6192	1335	441	343	564	688	717	85.2
	SD					NA	1137	1875	2322	622	154	67.2	191	309	422	56.7
	2-2 Old	141232	PO	60	004M	<LLOQ	2105	4169	2431	576	245	162	294	326	286	26.8
					005M	<LLOQ	3633	5741	2958	997	711	377	527	611	575	13.3
					006M	<LLOQ	3612	3287	1956	1147	543	248	251	392	432	19.5
	Mean					<LLOQ	3116	4399	2448	907	499	262	358	443	431	19.9
	SD					NA	876	1243	501	296	236	108	148	149	145	6.74

Fig. 9

10/17

Sequence	Polymorph ID	Animal ID	Actual dose (mg/kg)	Animal weight (kg)	Tmax (h)	Cmax (ng/mL)	AUC(0-t) (h*ng/mL)	AUC(0-∞) (h*ng/mL)	AUCext (%)	CL/F (mL/h/kg)	V/F (mL/kg)	T1/2 (h)
1-1 Old	141232	001M	60.98	11.5	0.25	4530	9000	9500	5.19	6420	58000	6.26
		002M	61.4	10.6	0.25	8010	21600	22000	1.39	2800	13900	3.46
		003M	60.6	11.4	0.25	5460	16900	17300	2.45	3490	22000	4.36
				n	3	3	3	3	3	3	3	3
				Arithmetic Mean*	0.25	6000	15900	16300	3.01	4240	31300	4.69
				SD	-	1800	6390	6300	1.96	1920	23500	1.43
				SE	-	1040	3690	3640	1.13	1110	13500	0.826
				Min	-	4530	9000	9500	1.39	2800	13900	3.46
				Max	-	8010	21600	22000	5.19	6420	58000	6.26
				CV%	-	30.1	40.3	38.7	65.1	45.4	74.9	30.5
				Geometric Mean	-	5830	14900	15300	2.60	3970	26100	4.55
				CI 95% Lower	-	-1760	-11600	-10800	-5.43	-4040	-69600	-1.46
				CI 95% Upper	-	13800	43300	43400	11.4	12500	132000	10.8
2-1 New	COEN4-091-M	004M	61.61	11.0	0.5	10100	17400	17800	2.25	3460	24500	4.91
		005M	61.96	10.6	0.25	9680	19600	21000	6.45	2950	24900	5.85
		006M	62.17	9.59	0.25	8940	16000	16200	0.975	3850	20000	3.60
				n	3	3	3	3	3	3	3	3
				Arithmetic Mean*	0.25	9580	17700	18300	3.22	3420	23100	4.79
				SD	-	593	1820	2450	2.86	448	2740	1.13
				SE	-	342	1050	1410	1.65	259	1580	0.652
				Min	-	8940	16000	16200	0.975	2950	20000	3.60
				Max	-	10100	19600	21000	6.45	3850	24900	5.85
				CV%	-	6.19	10.3	13.4	88.9	13.1	11.8	23.6
				Geometric Mean	-	9560	17600	18200	2.42	3400	23000	4.69
				CI 95% Lower	-	7030	9830	7790	-9.10	1490	11300	-0.0727
				CI 95% Upper	-	12100	25500	28800	15.5	5350	34900	9.65

Fig. 10

11/17

Sequence	Polymorph ID	Animal ID	Actual dose (mg/kg)	Animal weight (kg)	Tmax (h)	Cmax (ng/mL)	AUC(0-t) (h*ng/mL)	AUC(0-∞) (h*ng/mL)	AUCext (%)	CL/F (mL/h/kg)	V/F (mL/kg)	T1/2 (h)
1-2 New	COEN4-091-M	001M	63.47	11.5	0.25	13800	16200	16300	0.737	3880	19100	3.42
		002M	63.35	10.9	0.25	15000	31800	32200	1.51	1960	10100	3.58
		003M	63.81	11.4	0.5	13300	25600	26700	4.32	2390	20200	5.86
				n	3	3	3	3	3	3	3	3
				Arithmetic Mean*	0.25	14100	24500	25100	2.19	2740	16500	4.29
				SD	-	881	7830	8080	1.89	1010	5520	1.37
				SE	-	508	4520	4670	1.09	583	3190	0.790
				Min	-	13300	16200	16300	0.737	1960	10100	3.42
				Max	-	15000	31800	32200	4.32	3880	20200	5.86
				CV%	-	6.26	31.9	32.2	86.1	36.8	33.5	32.0
				Geometric Mean	-	14000	23600	24200	1.69	2630	15800	4.15
				CI 95% Lower	-	10300	-9150	-9660	-5.93	-1600	-7290	-1.61
				CI 95% Upper	-	17900	58200	59900	10.3	7090	40300	10.2
2-2 Old	141232	004M	60.33	10.9	0.5	4170	9150	9300	1.58	6490	35600	3.80
		005M	62.37	10.2	0.5	5740	15400	15500	0.298	4030	13900	2.39
		006M	61.03	9.50	0.25	3610	11100	11200	0.728	5440	22800	2.91
				n	3	3	3	3	3	3	3	3
				Arithmetic Mean*	0.5	4510	11900	12000	0.869	5320	24100	3.04
				SD	-	1100	3200	3150	0.654	1230	10900	0.714
				SE	-	638	1850	1820	0.377	711	6300	0.412
				Min	-	3610	9150	9300	0.298	4030	13900	2.39
				Max	-	5740	15400	15500	1.58	6490	35600	3.8
				CV%	-	24.5	26.9	26.3	75.2	23.2	45.2	23.5
				Geometric Mean	-	4420	11600	11700	0.700	5220	22500	2.98
				CI 95% Lower	-	-245	-1870	-1580	-1.94	18.4	-22800	-0.0379
				CI 95% Upper	-	9260	25700	25600	3.68	10600	71000	6.11

Fig.11

12/17

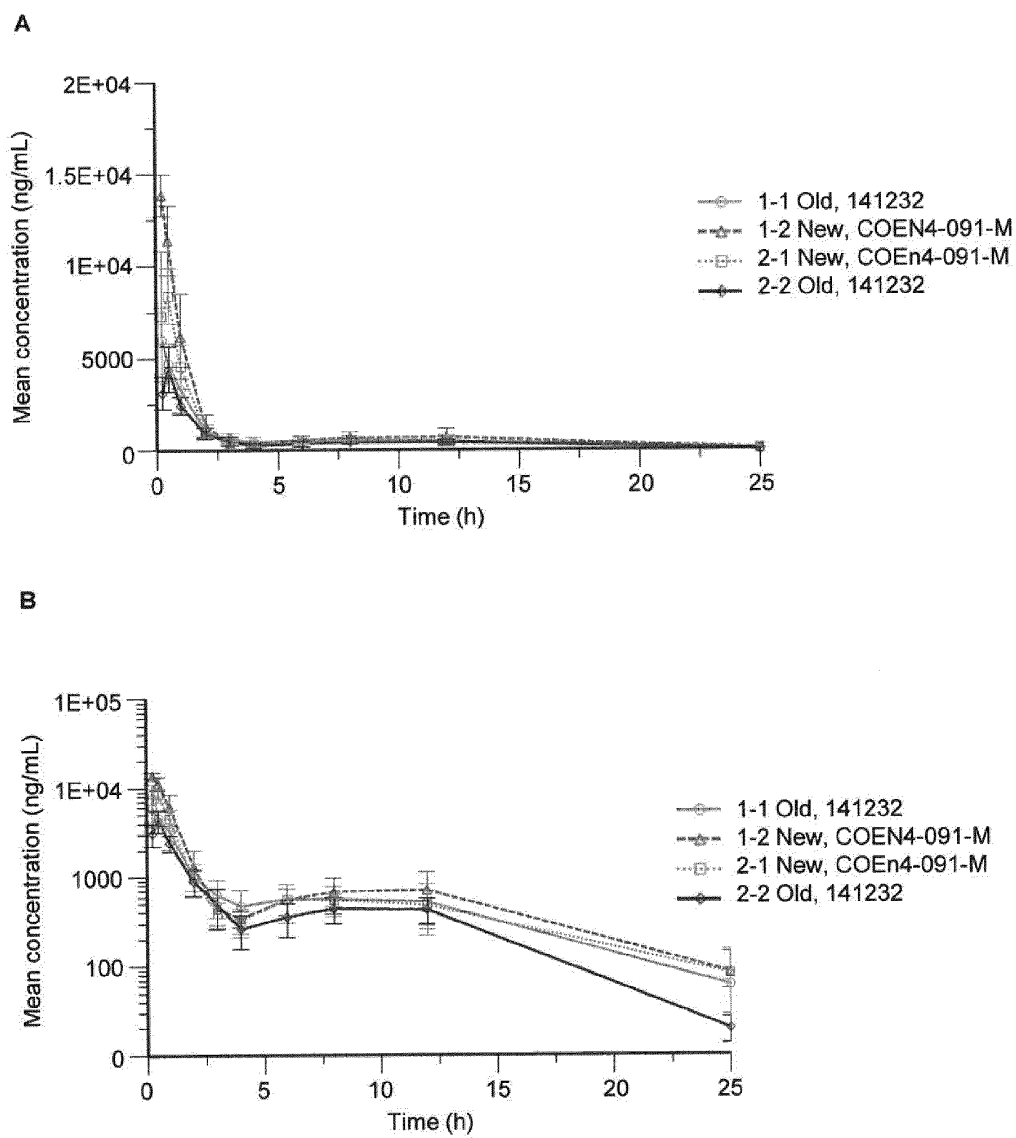


Fig. 12

13/17

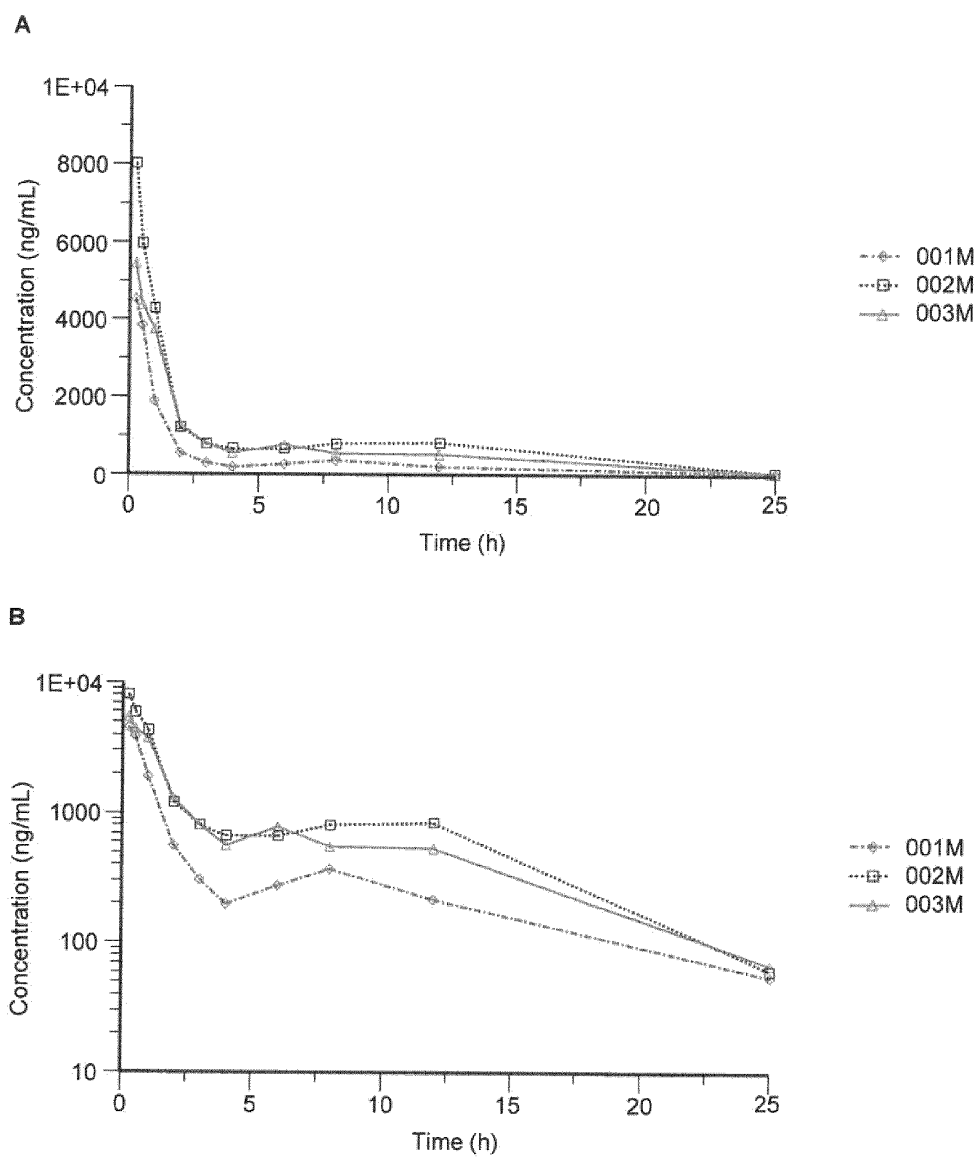


Fig. 13

14/17

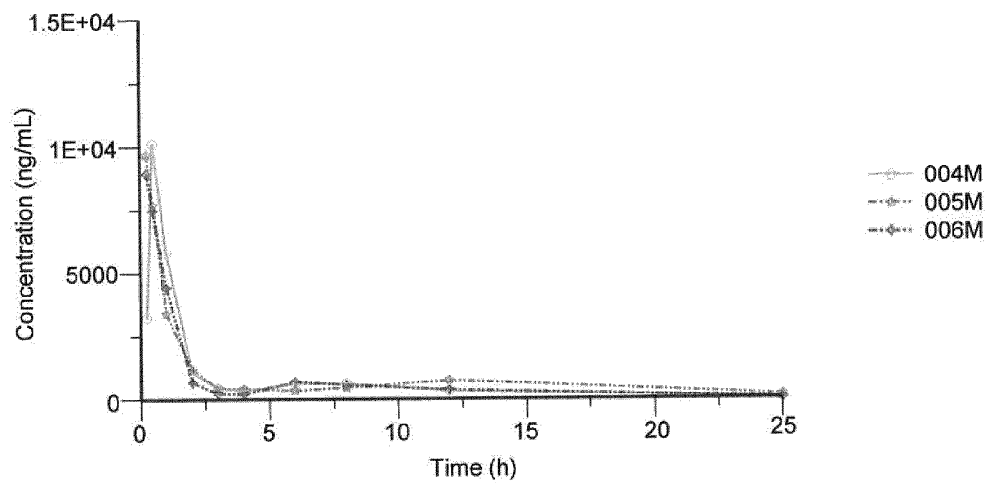
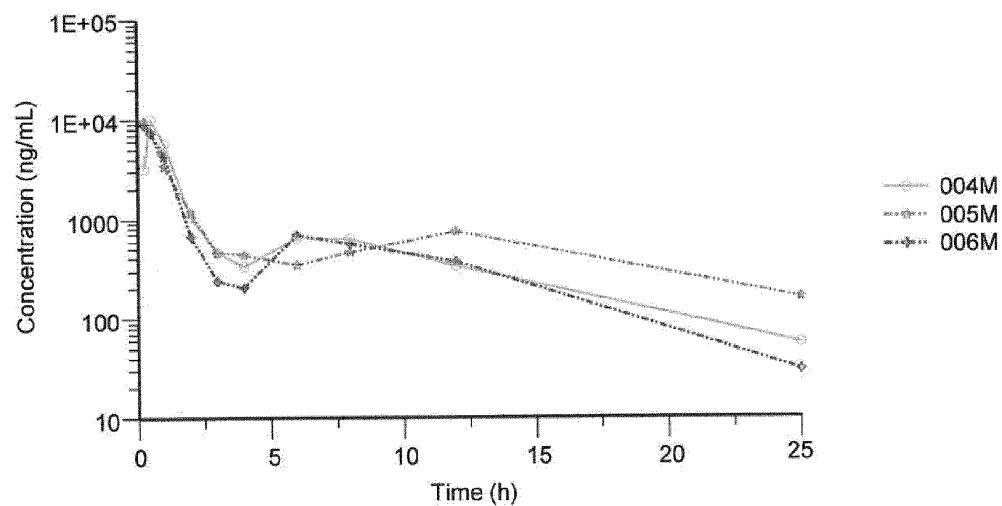
A**B**

Fig. 14

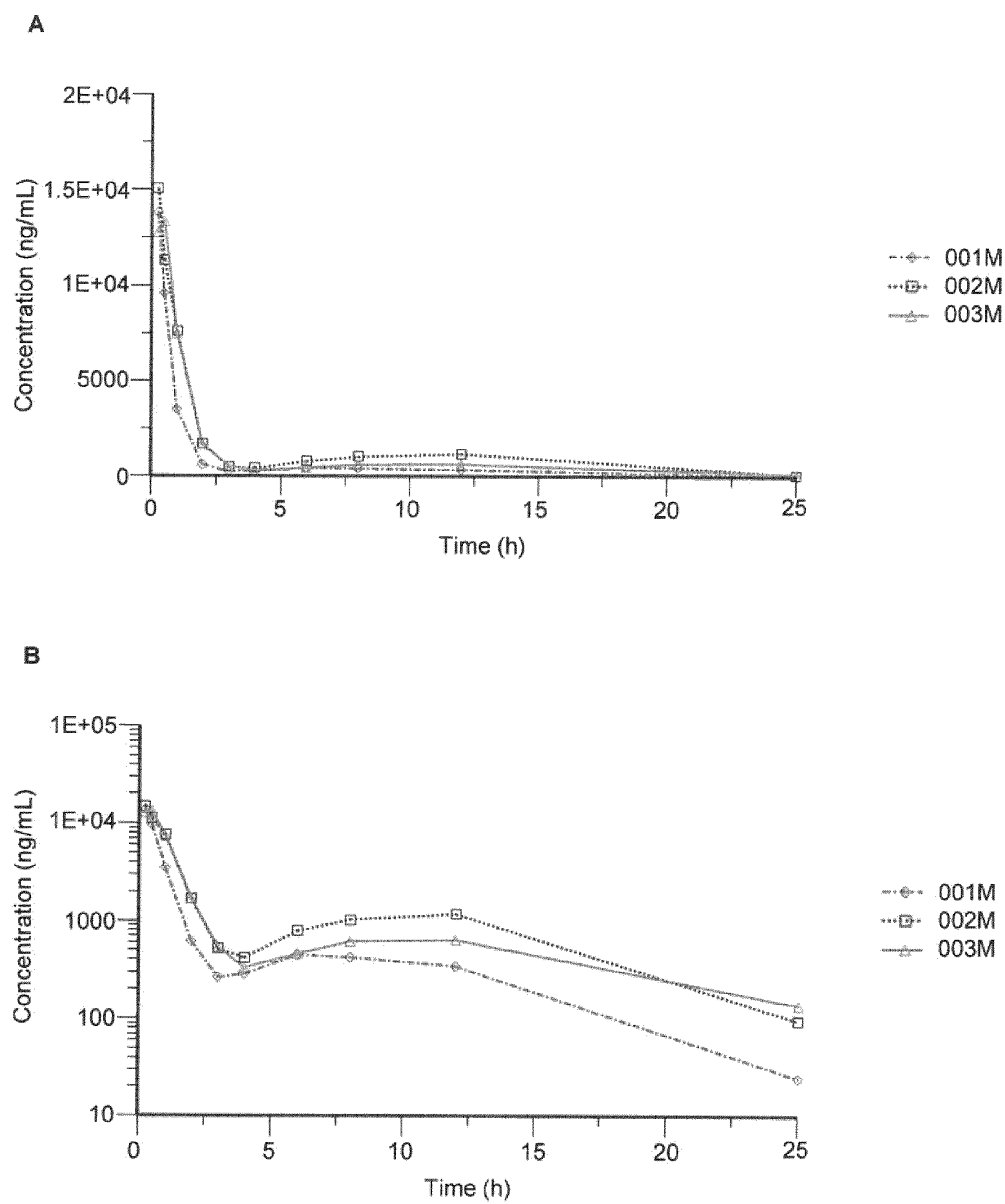


Fig. 15

16/17

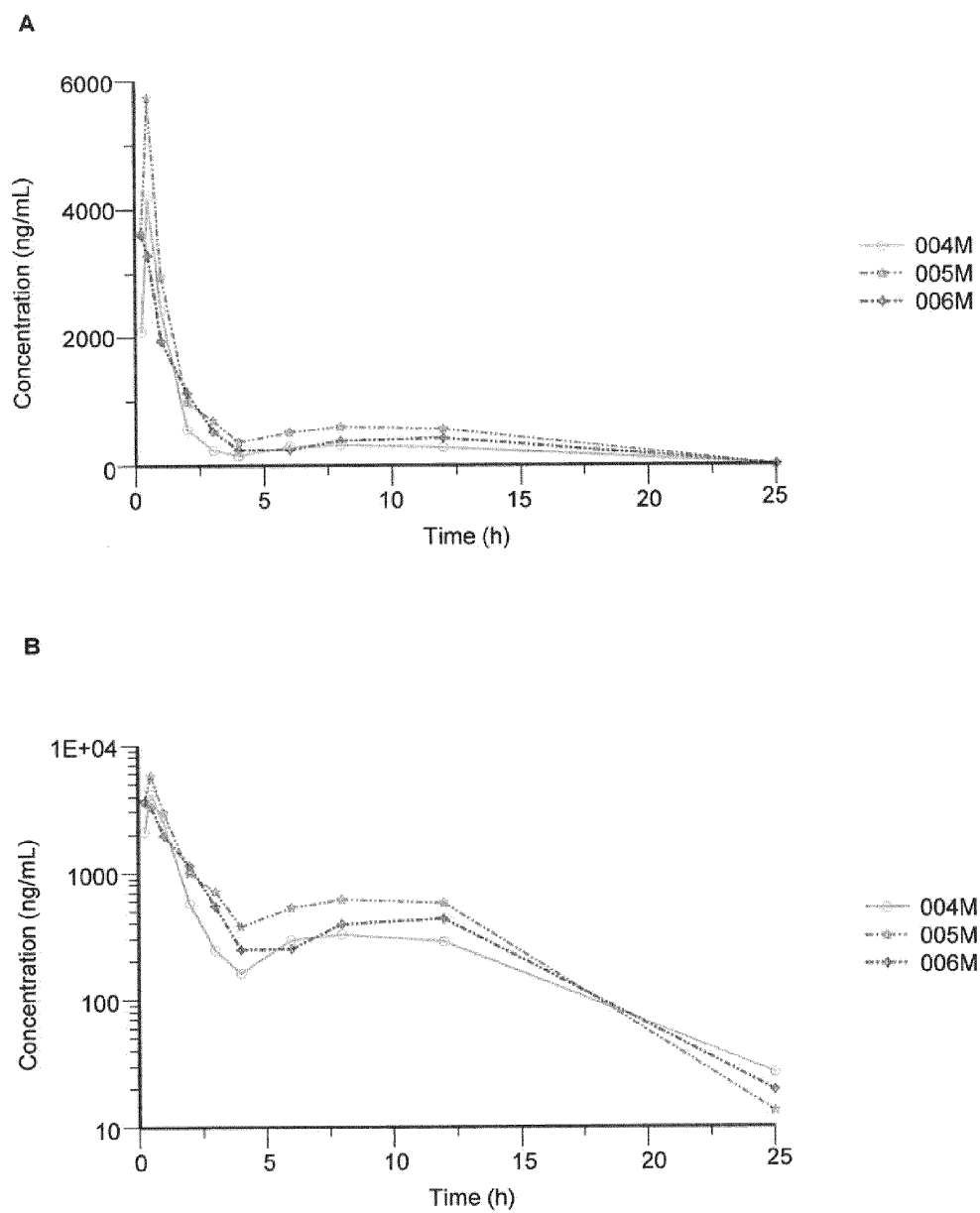


Fig. 16

17/17

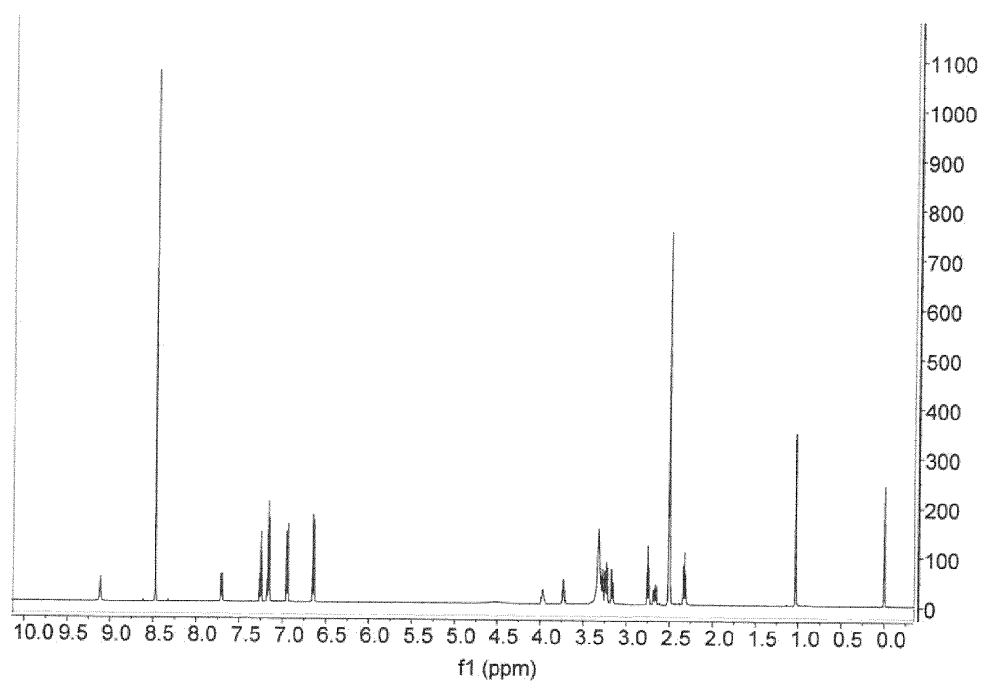


Fig. 17