



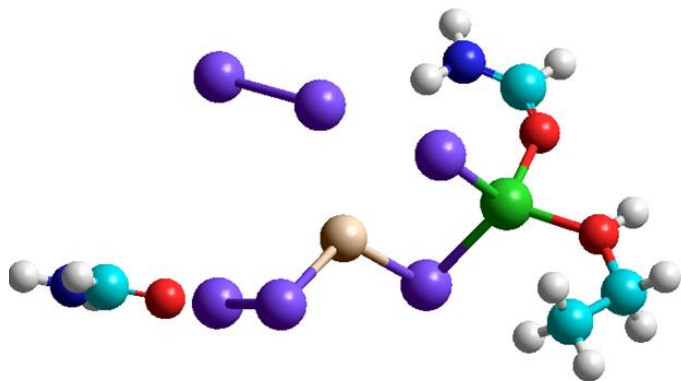
НАУЧНЫЙ ЦЕНТР
ПРОТИВОИНФЕКЦИОННЫХ
ПРЕПАРАТОВ

**Pharmacokinetics (PK) of anti-tuberculosis drug
(FS-1) on healthy volunteers: results
from the phase I trial**

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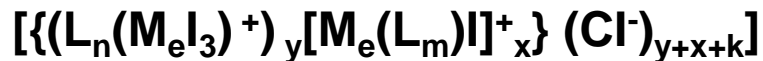
NEW DRUG APPLICATION – FS-1



Substance FS-1 is a complex (adduct) containing triiodide, molecular iodine and a positively charged ion, magnesium (+2) and lithium (+1). In the calculations, dextrin is replaced by ethanol, and peptide by amide.

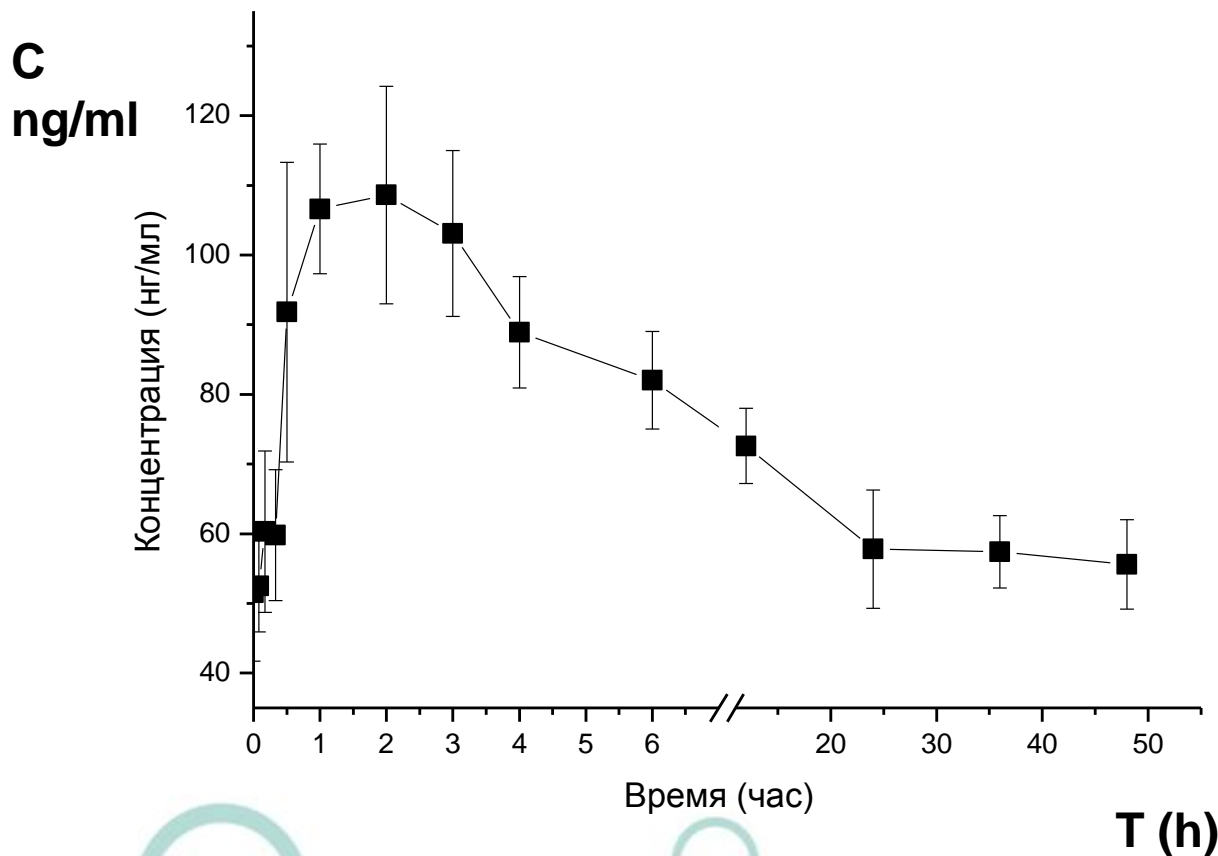
The resulting calculations of interatomic distance indicate that that iodine atoms, magnesium and lithium are located within the dextrin helix. Molecular iodine coordinates peptide located outside of dextrin helix. The peptide may also be externally coordinated by magnesium ion

O, N, C, I, Li, Mg





Averaged PK curve of FS-1 (dose 15 mg/kg)





Concentration (ng/ml) of FS-1 in blood plasma of healthy volunteers after single administration of 15 mg/kg administration

Время (час)	И668	И646	И681	И627	И679	И686	И234	И322		SD	CV %
1	2	3	4	5	6	7	8	9	10	11	12
0	45	66	51	38	52	44	65	51	51,5	9,8	19,05
0,08	51	60	54	46	56	40	58	55	52,5	6,6	12,63
0,17	66	55	60	44	-	50	70	77	60,3	11,6	19,22
0,33	65	43	76	56	61	55	62	60	59,8	9,4	15,69
0,5	135	95	106	89	65	84	73	87	91,8	21,5	23,45
1	124	102	112	96	101	112	98	108	106,6	9,3	8,70
2	94	109	126	90	135	106	112	97	108,6	15,6	14,40
3	91	112	96	88	122	114	99	103	103,1	11,9	11,57
4	87	79	86	80	102	98	88	91	88,9	8,0	9,01
1	2	3	4	5	6	7	8	9	10	11	12
6	88	76	70	82	92	79	86	83	82,0	7,0	8,52
12	80	70	66	68	70	76	80	71	72,6	5,4	7,39
24	50	72	64	44	56	60	60	56	57,8	8,5	14,74
36	60	66	55	50	60	56	52	60	57,4	5,2	8,98
48	52	68	56	48	56	50	61	54	55,6	6,4	11,53



PARMACOKINETIC PARAMETERS (PK) OF FS-1*

Three groups (n 27) volunteers were administered single oral dose of FS-1

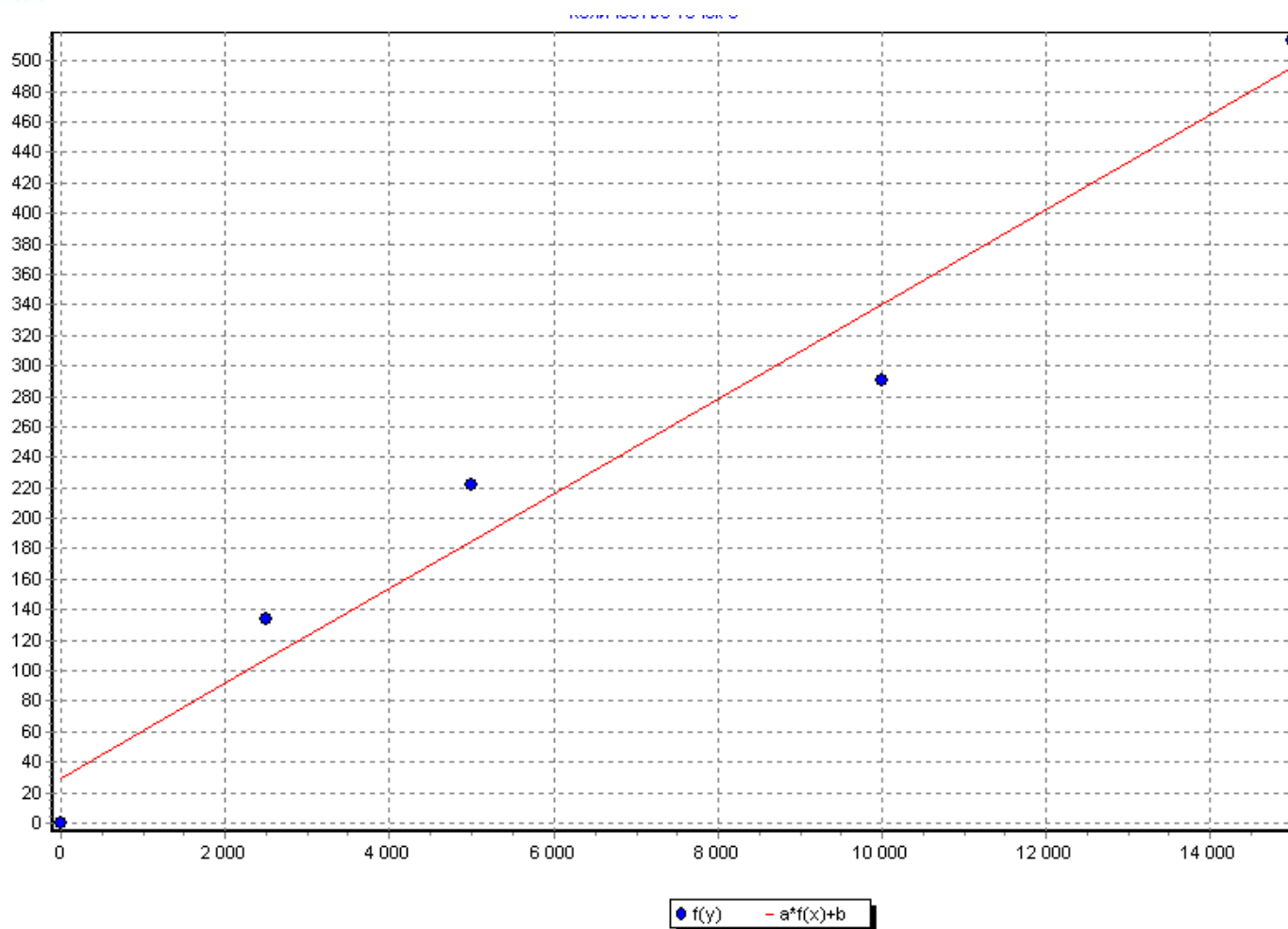
PK**	Dose of FS-1 (mg/kg)		
	5	10	15
AUC (ng*h/ml)	340	402	619
C _{max} (ng/ml)	29.6	41.0	54.4
Clirence (ml*h/kg)	13.4	25.8	24.3
T _{max} (h)	2.6	1.6	1.4
V _β (ml/kg)	338	586	536
T _{1/2} (h)	16	17	14
K _β (h)	0.04	0.03	0.06

* non binding with proteins of blood (freedom fraction)

** non-compartment model



Relationship AUC₀₋₂₄ from dose of FS-1





CONCLUSION

FS-1 PK parameters were consistent with preclinical studies.

Character of the relationship between the dose of the FS-1 and the AUC, as well as the constancy of FS-1 invariant PK parameters indicate that the dynamics of ADME of the drug is subject to the basic principles of linear pharmacokinetics.

Values microconstants adsorption rate, interchange tissue and blood and elimination found modeling methods indicate that the ratio between their values subject to the condition: $k_a > k_{10} \geq k_{12}, k_{21}$, suggests that the FS-1 does not tend to accumulate in tissues and organs.

It also indicates a middle volume of distribution values and the relationship between drug half-life drugs and the average time it retention.



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Thank you!



PK FS-1 observed by non-modal (MCM) and modal methods for dose 5 mg/kg

Линейный метод		Нелинейная регрессия		Метод MIX(Л)		Метод MIX(Н)		MCM	
A1	271.4433	A1	0	A1	171.8578	A1	0	AUC	339.6512
A2	14.41378	A2	0	A2	14.41378	A2	0	AUMC	7249.628
alfa	0.9242642	alfa	0	alfa	0.6063938	alfa	0	CL	14.72098
beta	0.04355504	beta	0	beta	0.04355504	beta	0	MRT	21.34433
Ka	1.132177	Ka	0	Ka	0.7482173	Ka	0	Vss	314.2096
AUC	372.1338	AUC	0	AUC	365.3882	AUC	0	beta	0.04355504
AUMC	7692.771	AUMC	0	AUMC	7732.668	AUMC	0	Rbeta	0.9560244
CL	13.43603	CL	0	CL	13.68408	CL	0	tau_1/2_beta	15.91428
MRT	20.67206	MRT	0	MRT	21.16289	MRT	0	Vbeta	337.9858
Vss	277.7504	Vss	0	Vss	289.5946	Vss	0	Линейный метод	
K12	0.5614747	K12	0	K12	0.3145345	K12	0	Ralfa	1
K21	0.2351507	K21	0	K21	0.20911	K21	0	Rbeta	0.9560244
K10	0.1711939	K10	0	K10	0.1263044	K10	0	RKa	0.9963917
Vbeta	308.4839	Vbeta	0	Vbeta	314.179	Vbeta	0	tau_1/2_beta	15.91428
C0	63.70703	C0	0	C0	46.15013	C0	0	tau_1/2_Ka	0.6122252
V1	78.48427	V1	0	V1	108.3421	V1	0		
SD	8.782172	SD	0	SD	4.347597	SD	0		



PK FS-1 observed by non-modal (MCM) and modal methods for dose 10 mg/kg

Линейный метод		Нелинейная регрессия		Метод MIX(Л)		Метод MIX(Н)		MCM	
A1	51.80246	A1	9868.506	A1	336.6416	A1	0	AUC	424.3667
A2	9.528211	A2	59.08352	A2	9.528211	A2	0	AUMC	8182.51
alfa	0.2322949	alfa	2.892027	alfa	0.4907712	alfa	0	CL	23.56453
beta	0.0341476	beta	0.1821147	beta	0.0341476	beta	0	MRT	19.2817
Ka	1.678101	Ka	2.876078	Ka	0.651683	Ka	0	Vss	454.3641
AUC	465.4855	AUC	285.388	AUC	433.7806	AUC	0	beta	0.0341476
AUMC	9109.517	AUMC	1780.482	AUMC	8753.873	AUMC	0	Rbeta	0.8423498
CL	21.48295	CL	35.04002	CL	23.05313	CL	0	tau_1/2_beta	20.29856
MRT	19.56993	MRT	6.238812	MRT	20.18041	MRT	0	Vbeta	690.0786
Vss	420.4197	Vss	218.6081	Vss	465.2217	Vss	0	Линейный метод	
K12	0.08208731	K12	-239.439	K12	0.2335935	K12	0	Ralfa	0.9566436
K21	0.06842055	K21	242.511	K21	0.07888726	K21	0	Rbeta	0.8423498
K10	0.1159347	K10	0.00217178	K10	0.2124381	K10	0	RKa	0.9725729
Vbeta	629.1202	Vbeta	192.4063	Vbeta	675.1025	Vbeta	0	tau_1/2_beta	20.29856
CO	53.96591	CO	0.6188816	CO	92.15153	CO	0	tau_1/2_Ka	0.4130544
V1	185.3022	V1	16158.18	V1	108.5169	V1	0		
SD	4.589258	SD	2.530743	SD	2.276794	SD	0		



PK FS-1 observed by non-modal (MCM) and modal methods for dose 15 mg/kg

Линейный метод		Нелинейная регрессия		Метод MIX(Л)		Метод MIX(Н)		MCM	
A1	52.3107	A1	74506.93	A1	57.95657	A1	506.9862	AUC	636.0173
A2	9.528211	A2	42.89239	A2	9.528211	A2	42.89239	AUMC	10031.57
alfa	0.1279766	alfa	0.8549264	alfa	0.1498646	alfa	0.7989523	CL	23.58426
beta	0.0341476	beta	0.08111726	beta	0.0341476	beta	0.08111726	MRT	15.77247
Ka	3.93188	Ka	0.8558291	Ka	1.870022	Ka	0.9316582	Vss	371.9822
AUC	672.0547	AUC	585.5917	AUC	629.6688	AUC	573.119	beta	0.0341476
AUMC	11361.26	AUMC	8002.095	AUMC	10732.5	AUMC	6679.325	Rbeta	0.8423498
CL	22.31961	CL	25.61512	CL	23.82205	CL	26.17257	tau_1/2_beta	20.29856
MRT	16.90526	MRT	13.66497	MRT	17.04468	MRT	11.65434	Vbeta	690.6566
Vss	377.3188	Vss	350.0299	Vss	406.0392	Vss	305.0241	Линейный метод	
K12	0.0238607	K12	0.3932569	K12	0.03306905	K12	0.3522395	Ralfa	0.9122975
K21	0.0489054	K21	0.3370065	K21	0.05142076	K21	0.3335017	Rbeta	0.8423498
K10	0.08935809	K10	0.2057803	K10	0.09952235	K10	0.1943283	RKa	0.9676813
Vbeta	653.6217	Vbeta	315.7789	Vbeta	697.6199	Vbeta	322.6511	tau_1/2_beta	20.29856
CO	60.05352	CO	117.4127	CO	62.66612	CO	111.3732	tau_1/2_Ka	0.176289
V1	249.7772	V1	127.7545	V1	239.3638	V1	134.6823		
SD	13.87754	SD	7.043182	SD	8.050648	SD	7.219998		