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多靶点偶联分子抗菌新药 TNP-2092 的II期临床试验结果

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丹诺医药简介

- 成立于2013年，临床阶段、全球性、专门从事**差异化**抗菌新药产品研发
- 三个产品进入II-III期临床试验阶段，适应症包括**医疗器械相关生物膜感染**、**肝硬化肝性脑病**和**幽门螺杆菌感染**
- 经验丰富的研发和顾问团队；团队包括国家级、江苏省和苏州市领军人才；顾问包括中美科学院院士和知名医学、法规、统计、药学和毒理等方面的专家
- 获得知名投资机构和国家**新药创制科技重大专项**支持

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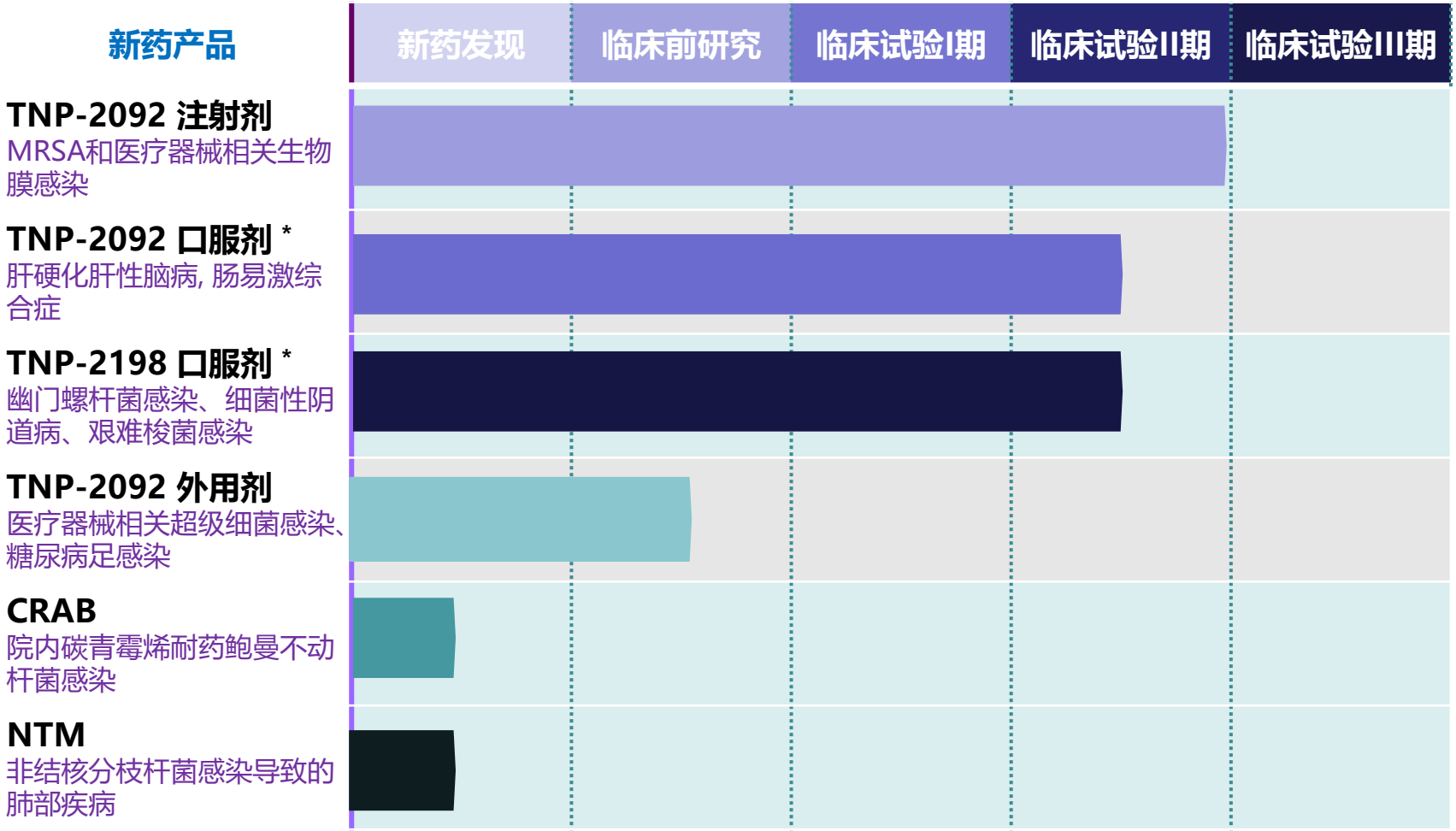
差异化新药研发产品线



* 国家十三五新药创制科技重大专项支持项目

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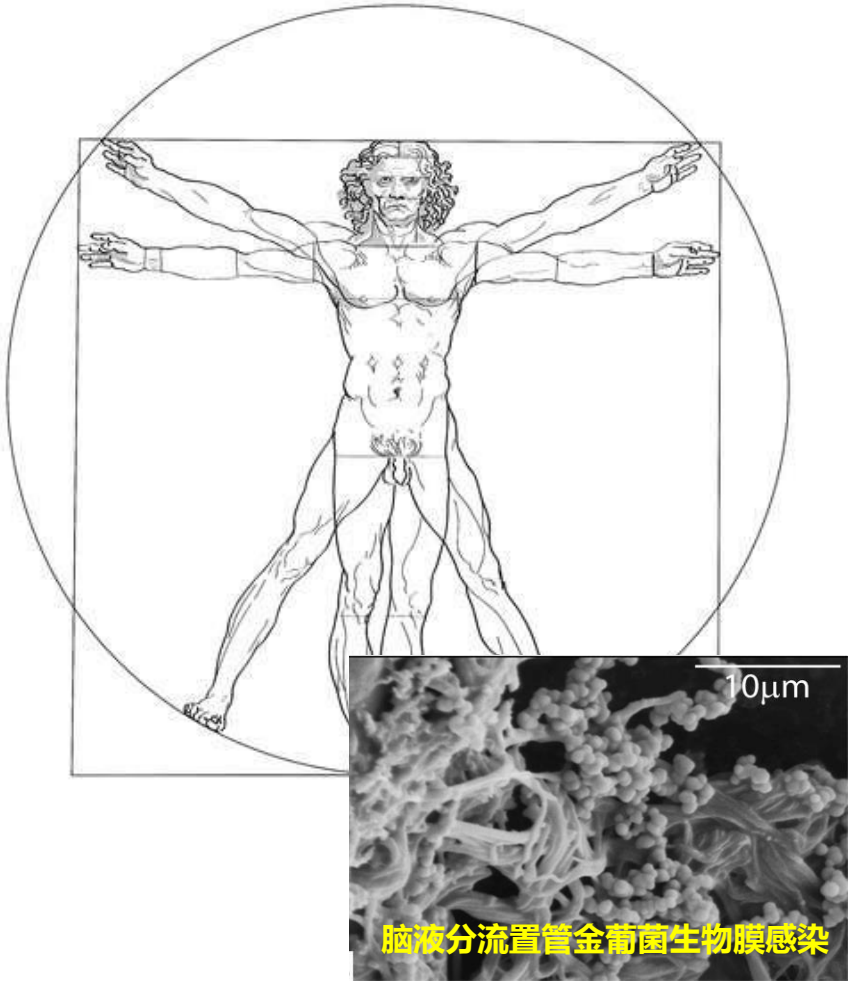
医疗器械相关生物膜感染

植入性医疗器械

脑脊髓液分流置管
鼓膜置管
气管插管
中心静脉导管
心脏起搏器
人工心脏瓣膜
乳房植入物
血管支架
外周血管导管
导尿管
人工关节
骨科植入物



医疗器械感染

- 美国医疗感染中有25.6%与植入性医疗器械相关
  - 每年170万院内感染与医疗器械相关，导致110亿美元的经济负担
- 细菌在器械表面形成**生物膜** (biofilm)
- 没有专门针对医疗器械相关生物膜感染开发的产品上市
- 现有抗菌药物治疗效果差，目前治疗以**手术置换**为主

Magill et al. N Engl J Med. 2014; 370 (13): 1198–1208.
Patel et al. Infect Dis Clin N Am 2018; 32: 915–929.
VanEpps JS, Younger JG. Implantable Device-Related Infection. *Shock*. 2016; 46(6): 597-608.

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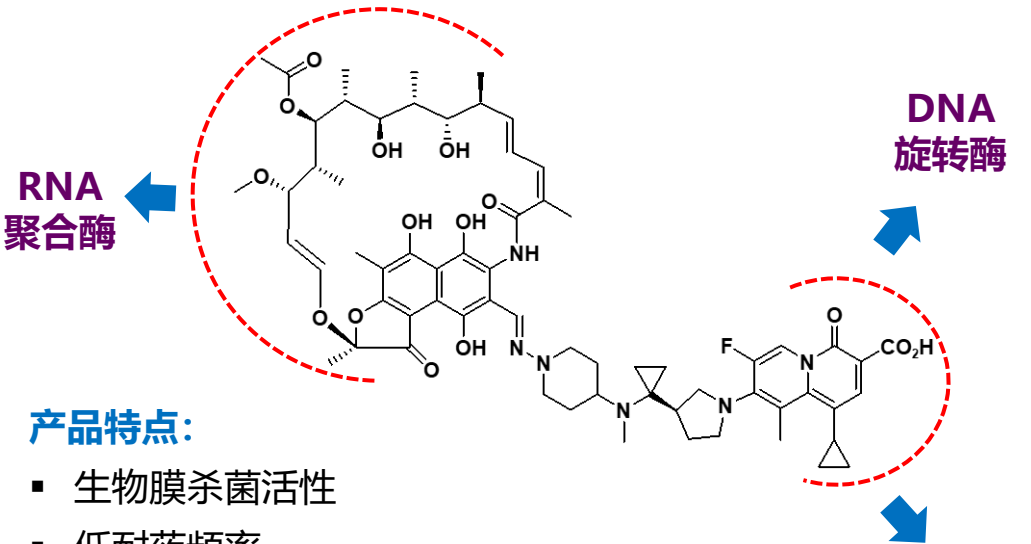
多靶点偶联分子 TNP-2092



产品特点：

- 生物膜杀菌活性
- 低耐药频率
- 药效协同作用
- 药代动力学和药物分布匹配性

产品剂型和目标适应症：

注射剂：医疗器械相关生物膜感染（临床II期完成/美国）

口服剂：肝硬化高血氨症和肝性脑病（临床II期入组/中国）

外用剂：糖尿病足感染（IND准备）

TNP-2092是专门针对生物膜感染设计的多靶点偶联分子，利用利福霉素及其靶点RNA聚合酶在治疗生物膜感染方面的优势，解决利福霉素的耐药问题

- TNP-2092作用于细菌的3个生物膜生长状态的重要靶点: RNA 聚合酶、DNA 旋转酶和 DNA 拓扑异构酶 IV
- 克服耐药（包括MRSA和喹诺酮耐药），具有较低的自发耐药频率（$<10^{-12}$）
- 同利福平+喹诺酮药物组合相比，对医疗器械相关生物膜感染具有更强的协同作用和体外、体内杀菌活性
- 具有更匹配的药代动力学特性和更好的安全耐受性

Ma Z, Lynch AS, . J. Med. Chem. 2016; 59 (14): 6645–6657.

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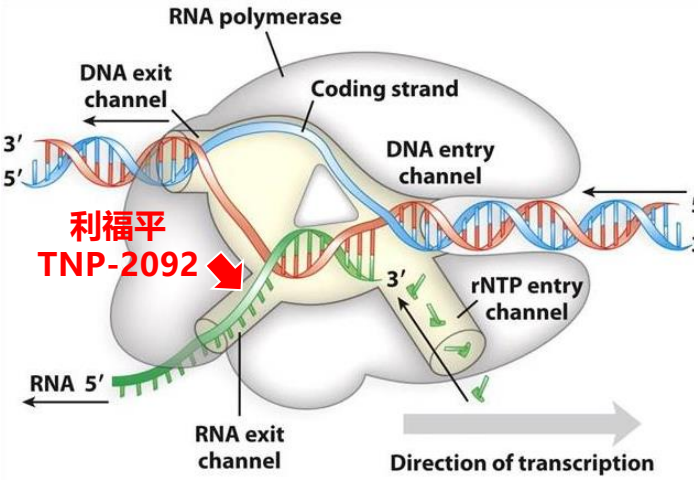
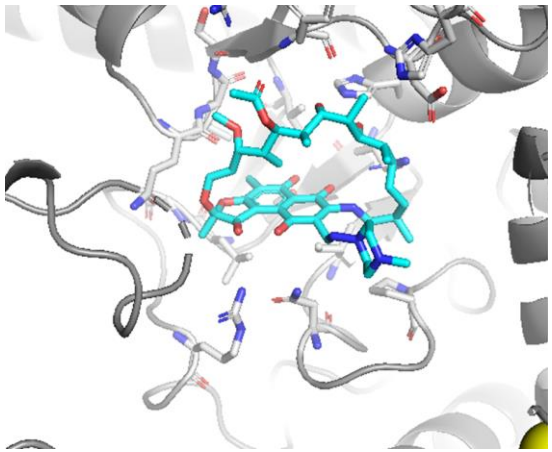
TNP-2092 具有独特作用机制

TNP-2092与细菌RNA聚合酶结合高分辨单晶结构

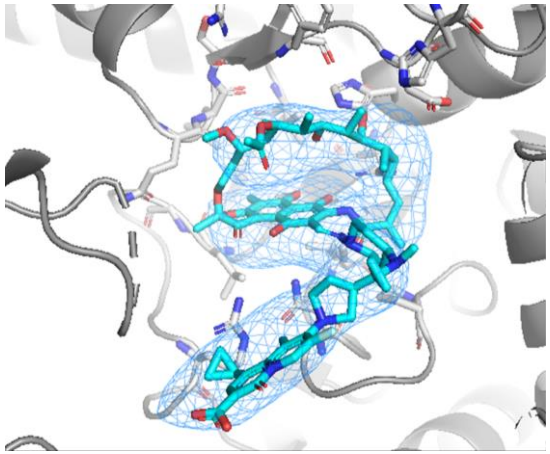
- 利福平结合在RNA聚合酶的RNA退出通道位点，阻碍RNA链的延长
- TNP-2092除与RNA聚合酶作用外，还与DNA模板链作用，防止DNA平移



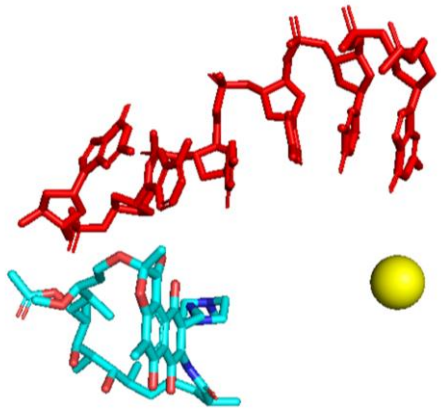
利福平-RNA聚合酶



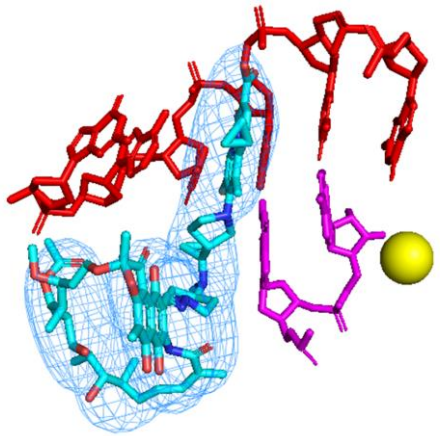
TNP-2092-RNA聚合酶



利福平-DNA



TNP-2092-DNA



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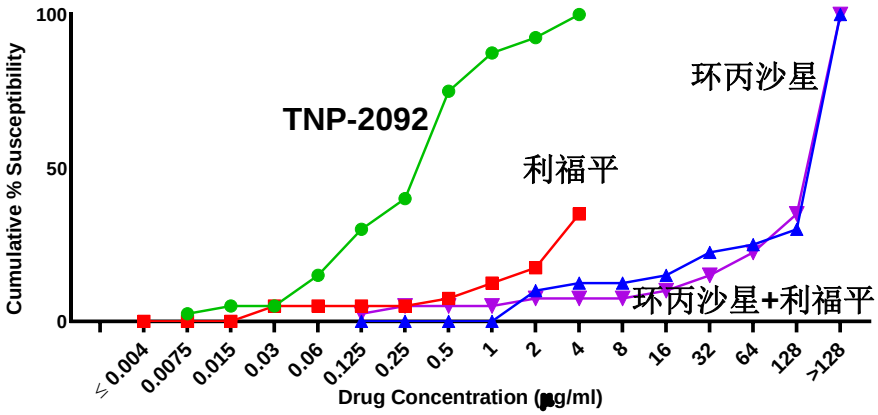
TNP-2092 生物膜杀菌活性

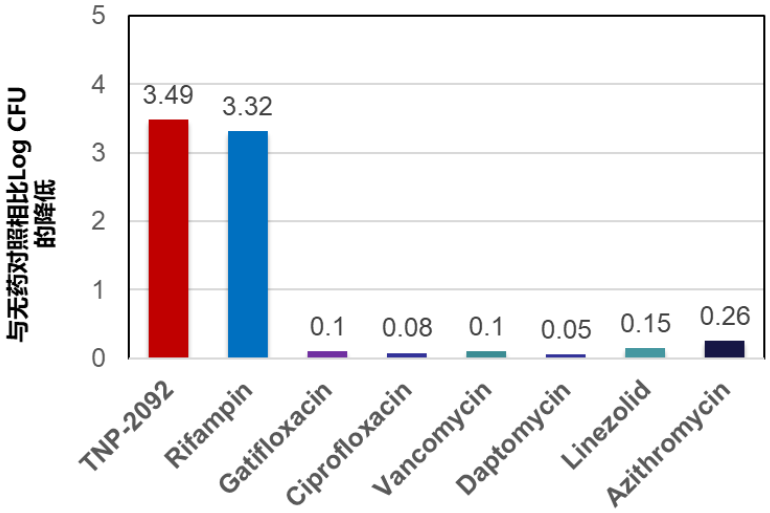
TNP-2092对40株人工关节感染相关金葡菌（20 MRSA + 20 MSSA）的体外生物膜杀菌活性



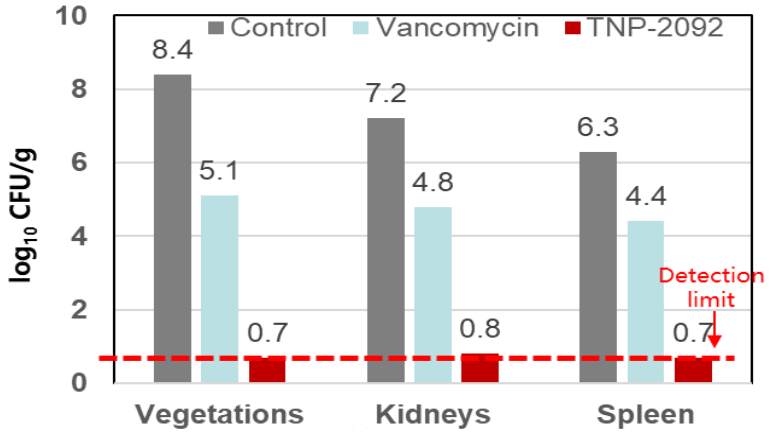
药物	对人工关节感染临床菌株的最低生物膜杀菌浓度 $MBBC_{90}$	
	金葡菌（40株）	表皮葡萄球菌（40株）
TNP-2092	2	0.25
利福平	>4	>4
环丙沙星	>128	>128
利福平+环丙沙星	>128	>128
达托霉素	16	8
万古霉素	>128	>128

大鼠中心静脉导管金葡菌生物膜感染模型

(所有药物剂量均为10 mg/kg)



新西兰兔心脏瓣膜MRSA生物膜感染模型



Patel R, et al. Diagnostic Microbiology and Infectious Disease. 2020; 97: 115040.

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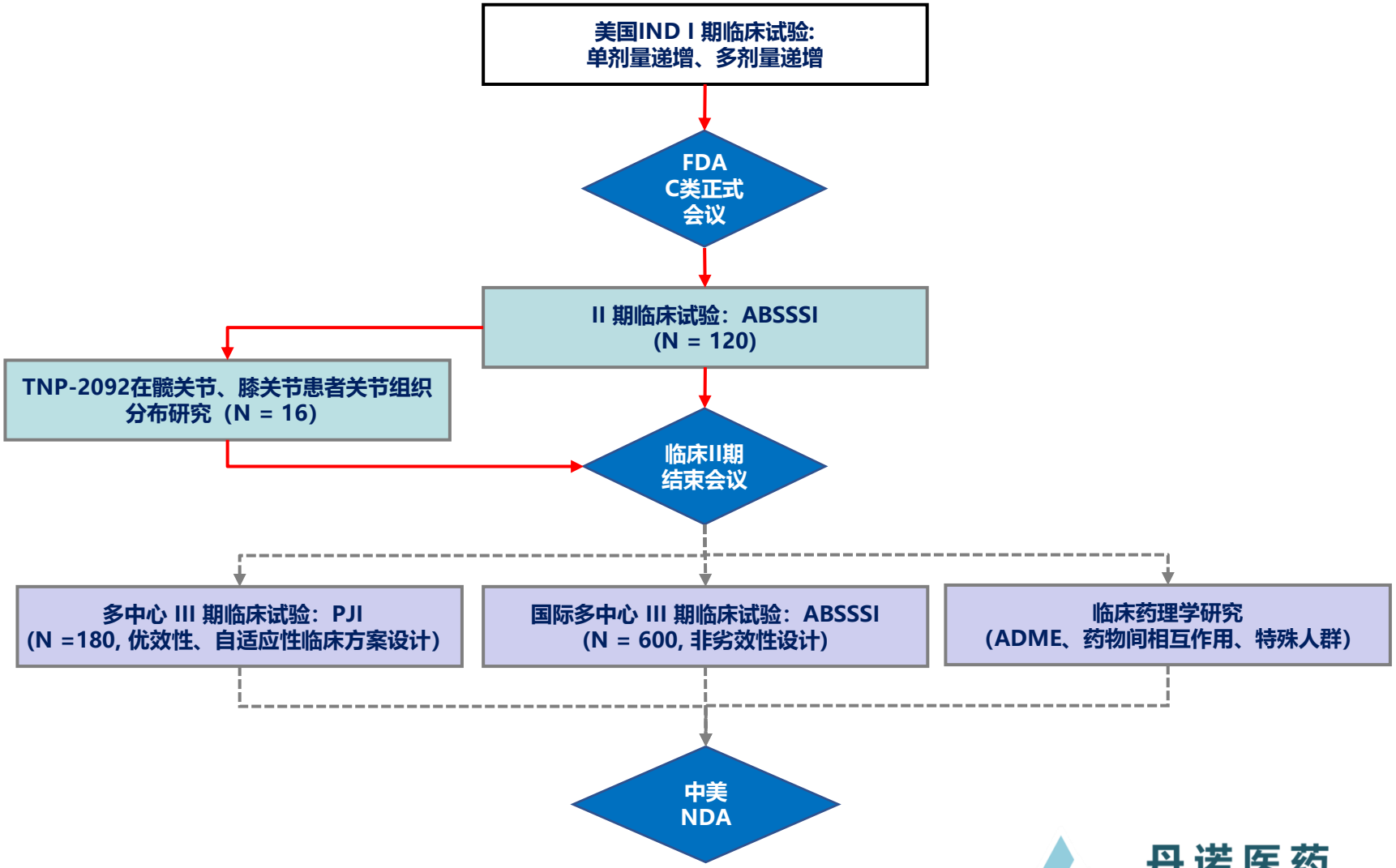
TNP-2092 注射剂临床开发计划



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TNP-2092 注射剂临床试验

目前已经完成了3项TNP-2092注射剂的临床试验，并获得美国FDA的QIDP、快速通道和孤儿药资格认定

临床试验	临床阶段	受试者例数	方案设计	主要结果
单剂量递增（SAD）	I期	64	单中心、随机、研究者盲、安慰剂对照试验；设置7个剂量组10至400 mg递增，静脉注射给药，每组8例受试者，3:1随机分配	安全性良好；PK随剂量递增增加；300mg 达到预测的有效暴露量
多剂量递增（MAD）	I期	49	单中心、随机、研究者盲、安慰剂对照试验；设置3个剂量组 50，100 和 300 mg，每天两次、连续14天静脉注射给药，每组16例受试者，3:1随机分配	安全性良好；PK随剂量递增增加；300mg 达到预测的有效暴露量
急性细菌性皮肤和皮肤结构感染（ABSSSI）	II期	120	多中心、随机、双盲、阳性对照试验，300 mg、BID、3-14天疗程，入组120例ABSSSI患者，按2:1随机分配到TNP-2092和万古霉素对照组	完成
TNP-2092 在膝关节/髋关节组织中的分布	I期	16	单中心、开放试验评价单剂量给药 TNP-2092 (300 mg, IV) 在膝或髋关节中的分布和药代动力学研究	进行中

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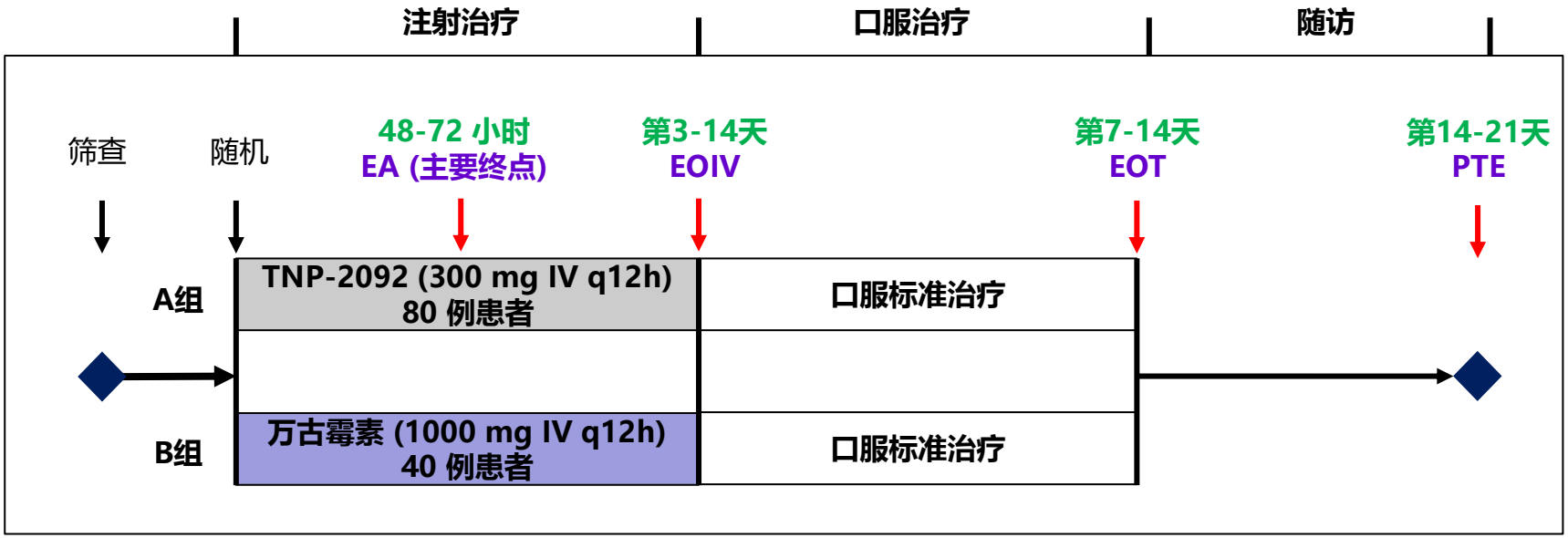
TNP-2092 注射剂II期临床试验方案

在美国IND下开展的一项多中心、随机、双盲、万古霉素对照的II期临床试验，治疗急性细菌性皮肤和皮肤结构感染（ABSSSI）



访视时间:

EA: 早期评价 (治疗开始后48-72小时)
EOIV: 注射剂治疗结束 (治疗开始后3-14天)
EOT: 治疗结束 (治疗开始后7-14天)
PTE: 治疗后评价 (治疗结束后7-14天)

研究人群:

ITT: 意向治疗 (所有随机患者)
mITT: 改良意向治疗 (排除革兰氏阴性菌感染)
Micro-ITT:微生物学意向治疗 (基线ABSSSI相关革兰氏阳性菌培养成功)
CE: 临床可评估 (完成>80%研究药物、治疗开始至评估结束没有使用其它有效系统抗菌药物、无主要方案违背)

研究终点： 1）安全耐受性，2）PK（D1和EOIV），3）疗效 (ITT、mITT,、micro-ITT、CE)

FDA Guidance for Industry：Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment （2013）

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人口统计和基线特征（ITT人群）

	TNP-2092 (N=80) n (%)	Vancomycin (N=40) n (%)	Total (N=120) n (%)
Age			
Mean ± standard deviation	41.4 (11.72)	42.7 (13.16)	41.9 (12.18)
Median	39.0	41.5	40.5
Minimum, maximum	21, 68	20, 75	20, 75
Race			
White, n (%)	70 (87.5)	32 (80.0)	102 (85.0)
African American, n (%)	5 (6.3)	4 (10.0)	9 (7.5)
American Indian/Alaskan Native, n (%)	1 (1.3)	3 (7.5)	4 (3.3)
Other, n (%)	4 (5.0)	1 (2.5)	5 (4.2)
Ethnicity			
Hispanic or Latino, n (%)	32 (40.0)	17 (42.5)	49 (40.8)
Not Hispanic or Latino, n (%)	48 (60.0)	23 (57.5)	71 (59.2)
Gender			
Male, n (%)	61 (76.3)	26 (65.0)	87 (72.5)
Female, n (%)	19 (23.8)	14 (35.0)	33 (27.5)
Height			
Mean ± standard deviation	173.5 (9.46)	170.5 (8.32)	172.5 (9.17)
Median	174.0	170.0	172.9
Minimum, maximum	147, 196	154, 183	147, 196
Body mass index (kg/m2)			
Mean ± standard deviation	24.1 (2.98)	24.8 (3.47)	24.4 (3.15)
Median	24	24	24
Minimum, maximum	17.8, 29.9	15.9, 29.8	15.9, 29.9
Weight (kg)			
Mean ± standard deviation	72.8 (11.81)	72.7 (14.43)	72.8 (12.68)
Median	71.7	73.8	71.7
Minimum, maximum	47, 108	40, 100	40, 108

ITT = intent-to-treat
N = number of subjects in the ITT population
n = number of subjects in the specific category

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基线病原体鉴定（Micro-ITT人群）

	TNP-2092 (N=51) n (%)	Vancomycin (N=29) n (%)
Gram-positive organisms (aerobes)	47 (92.2)	29 (100.0)
Staphylococcus aureus [a]	41 (80.4)	23 (79.3)
Methicillin-resistant S. aureus (MRSA)	32 (62.7)	19 (65.5)
Methicillin-susceptible S. aureus (MSSA)	9 (17.6)	4 (13.8)
Ciprofloxacin-resistant (CRSA)	29 (56.9)	18 (62.1)
Ciprofloxacin-susceptible (CSSA)	12 (23.5)	5 (17.2)
Rifampin-susceptible (RSSA)	40 (78.4)	23 (79.3)
Streptococcus anginosus	7 (13.7)	5 (17.2)
Streptococcus pyogenes	2 (3.9)	5 (17.2)
Streptococcus dysgalactiae	1 (2.0)	0
Streptococcus mitis	1 (2.0)	0
Streptococcus vestibularis	1 (2.0)	0
Gram-negative organisms (aerobes)	6 (11.8)	2 (6.9)
Eikenella corrodens	3 (5.9)	0
Haemophilus parainfluenzae	2 (3.9)	0
Aggregatibacter aphrophilus	1 (2.0)	0
Enterobacter cloacae	1 (2.0)	0
Proteus mirabilis	1 (2.0)	0
Klebsiella oxytoca	0	1 (3.4)
Pseudomonas aeruginosa	0	1 (3.4)
Gram-positive organisms (anaerobes)	5 (9.8)	1 (3.4)
Gram-negative organisms (anaerobes)	4 (7.8)	0

早期治疗（48-72小时）治疗应答率

ITT	TNP-2092 (N = 80)		Vancomycin (N = 40)		Difference
	n (%)	95% CI[a]	n (%)	95% CI[a]	95% CI[b]
Responder	61 (76.3)	65.4, 85.1	27 (67.5)	50.9, 81.4	8.7 (-7.7, 26.5)
Nonresponder	4 (5.0)	--	3 (7.5)	--	--
Indeterminate	15 (18.8)	--	10 (25.0)	--	--

mITT	TNP-2092 (N = 78)		Vancomycin (N = 40)		Difference
	n (%)	95% CI[a]	n (%)	95% CI[a]	95% CI[b]
Responder	60 (76.9)	66.0, 85.7	27 (67.5)	50.9, 81.4	9.4 (-7.0, 27.2)
Nonresponder	4 (5.1)	--	3 (7.5)	--	--
Indeterminate	14 (17.9)	--	10 (25.0)	--	--

Micro-ITT	TNP-2092 (N=51)		Vancomycin (N = 29)		Difference
	n (%)	95% CI[a]	n (%)	95% CI[a]	95% CI[b]
Responder	41 (80.4)	66.9, 90.2	19 (65.5)	45.7, 82.1	14.9 (-4.9, 35.7)
Nonresponder	3 (5.9)	--	2 (6.9)	--	--
Indeterminate	7 (13.7)	--	8 (27.6)	--	--

CI = Confidence Interval; EA = Early Assessment; N = Number of subjects in the micro-ITT Population; n = Number of subjects within a specific category

[a] 95% CI for responder rate using Exact (Clopper-Pearson) Confidence Limits.

[b] Difference in responder rate for TNP-2092 minus the responder rate for vancomycin and the CI for this difference is based on Miettinen-Nurminen method.

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按基线病原菌分类的早期治疗应答率

Class Pathogen	TNP-2092 (N = 51)		Vancomycin (N = 29)	
	N1	Responder n (%)	N1	Responder n (%)
Gram-positive aerobes	47	39 (83.0)	29	19 (65.5)
Staphylococcus aureus	41	33 (80.5)	23	13 (56.5)
Methicillin-resistant (MRSA)	32	25 (78.1)	19	11 (57.9)
Methicillin-susceptible (MSSA)	9	8 (88.9)	4	2 (50.0)
Ciprofloxacin-resistant (CRSA)	29	22 (75.9)	18	10 (55.6)
Ciprofloxacin-susceptible (CSSA)	12	10 (83.3)	5	3 (60.0)
Rifampin-susceptible (RSSA)	40	32 (80.0)	23	13 (56.5)
Streptococcus anginosus group	7	7 (100.0)	5	5 (100.0)
Streptococcus pyogenes	2	2 (100.0)	5	2 (40.0)
Streptococcus mitis group	1	1 (100.0)	0	0
Streptococcus vestibularis	1	1 (100.0)	0	0
Streptococcus dysgalactiae	1	0	0	0
Gram-negative aerobes	6	5 (83.3)	2	1 (50.0)
Eikenella corrodens	3	2 (66.7)	0	0
Haemophilus parainfluenzae	2	2 (100.0)	0	0
Aggregatibacter aphrophilus	1	1 (100.0)	0	0
Enterobacter cloacae	1	1 (100.0)	0	0
Klebsiella oxytoca	0	0	1	1 (100.0)
Proteus mirabilis	1	1 (100.0)	0	0
Pseudomonas aeruginosa	0		1	0
Gram-positive anaerobes	5	3 (60.0)	1	1 (100.0)
Gram-negative anaerobes	4	4 (100.0)	0	0

治疗结束（EOT）研究者判断治疗成功率

Population Response Category	TNP-2092 n (%)	 95% CI[a]	Vancomycin n (%)	 95% CI[a]	Difference 95% CI[b]
mITT					
N1	78		40		
Success	68 (87.2)	77.7, 93.7	31 (77.5)	61.5, 89.2	9.7 (-4.1, 26.1)
Failure	2 (2.6)	--	3 (7.5)	--	
Indeterminate	8 (10.3)	--	6 (15.0)	--	
Micro-ITT					
N1	51		29		
Success	45 (88.2)	76.1, 95.6	23 (79.3)	60.3, 92.0	8.9 (-7.2, 28.2)
Failure	2 (3.9)	--	1 (3.4)	--	
Indeterminate	4 (7.8)	--	5 (17.2)	--	
CE-EOT					
N1	59		28		
Success	57 (96.6)	88.3, 99.6	26 (92.9)	76.5, 99.1	3.8 (-5.9, 19.7)
Failure	2 (3.4)	--	2 (7.1)	--	

CI = Confidence Interval; EOIV = End of intravenous infusion; EOT = End of Treatment; N1 = Number of subjects in the specified Population. n = Number of subjects within a specific category

[a] 95% CI for responder rate using Exact (Clopper-Pearson) Confidence Limits.
[b] Difference in responder rate for TNP-2092 minus the responder rate for vancomycin and the CI for this difference is based on Miettinen-Nurminen method.

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随访（PTE）研究者判断治疗成功率

Population Response Category	TNP-2092 n (%)	 95% CI[a]	Vancomycin n (%)	 95% CI[a]	Difference 95% CI[b]
mITT					
N1	78		40		
Success	62 (79.5)	68.8, 87.8	31 (77.5)	61.5, 89.2	2.0 (-12.8, 19.0)
Failure	2 (2.6)	--	3 (7.5)	--	
Indeterminate	14 (17.9)	--	6 (15.0)	--	
Micro-ITT					
N1	51		29		
Success	40 (78.4)	64.7, 88.7	23 (79.3)	60.3, 92.0	-0.9 (-18.4, 19.4)
Failure	2 (3.9)	--	1 (3.4)	--	
Indeterminate	9(17.6)	--	5 (17.2)	--	
CE-PTE					
N1	56		27		
Success	54 (96.4)	87.7, 99.6	25 (92.6)	75.7, 99.1	3.8 (-6.3, 20.3)
Failure	2 (3.6)	--	2 (7.4)	--	

CI = Confidence Interval; EOIV = End of intravenous infusion; EOT = End of Treatment; N1 = Number of subjects in the specified population. n = Number of subjects within a specific category.

[a] 95% CI for responder rate using Exact (Clopper-Pearson) Confidence Limits.

[b] Difference in responder rate for TNP-2092 minus the responder rate for Vancomycin and the CI for this difference is based on Miettinen-Nurminen method.

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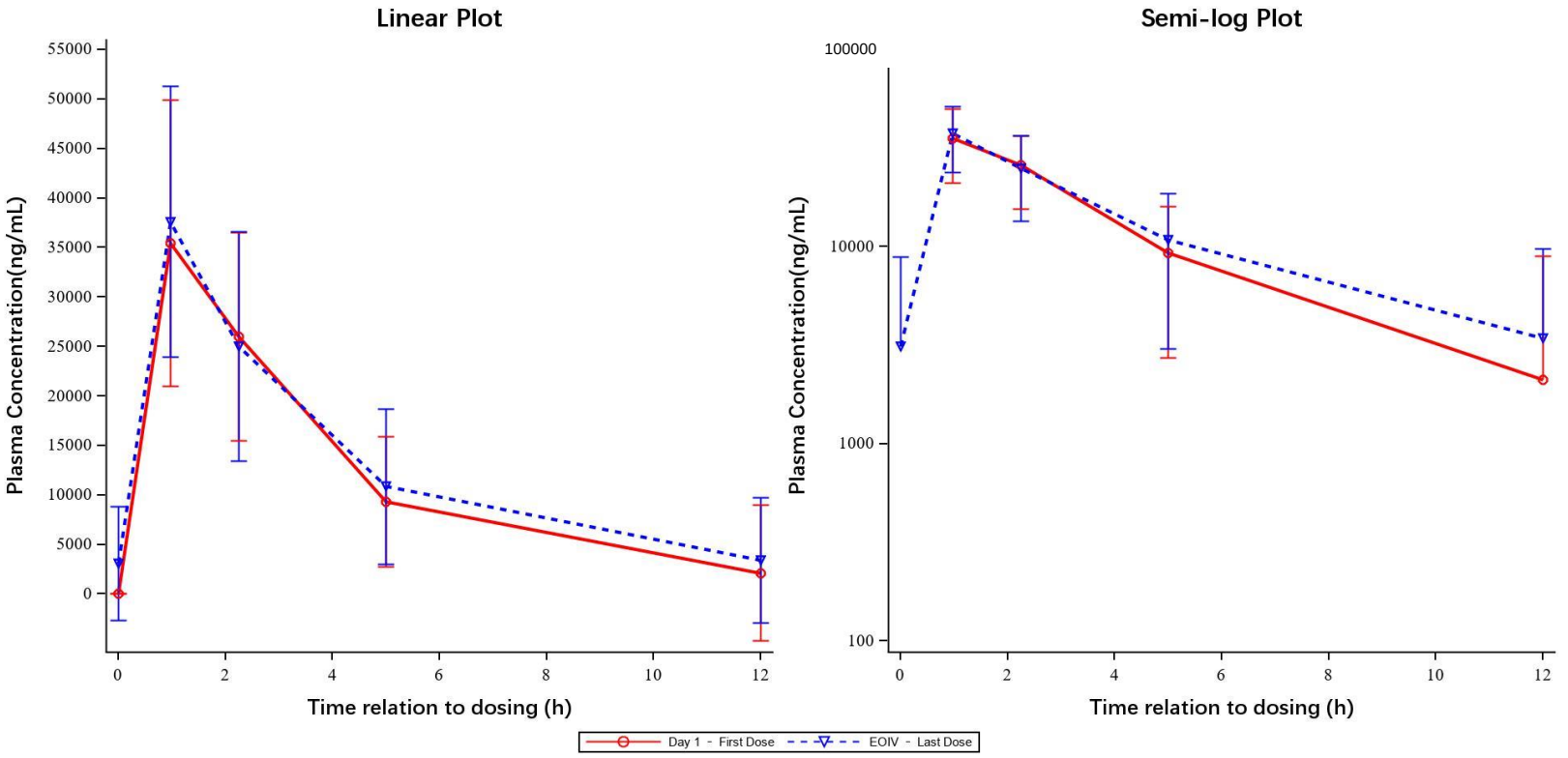
药代动力学

药代动力学人群中平均血浆浓度-时间曲线



Note: Mean of PK concentrations is plotted against scheduled time point. Mean +/- SD is presented.
<DIRECTORY PATH>: listing: 16.2.10.1 dataset: adam.adpc program name: f_14_3_5_1_1.sas output: f_14_3_5_1_1.rtf executed date: 2020-09-05 21:08

PK/PD分析：在300mg q12h 剂量下，100%药代动力学人群达到 $AUC_{0\text{-}24}$ > 50,000 h•ng/mL 的暴露量（动物模型预测的治疗生物膜感染所需的暴露量）

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不良事件发生率（安全性人群）

	TNP-2092 (N = 78) n (%)	Vancomycin (N = 39) n (%)
Number of subjects who experienced at least one:		
Adverse event (AE)	36 (46.2)	19 (48.7)
Treatment-emergent AE (TEAE)	36 (46.2)	16 (41.0)
TEAE related to study drug	19 (24.4)	4 (10.3)
Severe TEAE	1 (1.3)	1 (2.6)
TEAE leading to premature discontinuation of study drug	2 (2.6)	2 (5.1)
Serious TEAE (SAE)	1 (1.3)	2 (5.1)
SAE related to study drug	0 (0.0)	0 (0.0)
SAE leading to premature discontinuation of study drug	1 (1.3)	1 (2.6)

N=Number of subjects in the Safety Population; n=Number of subjects in the specific category; TEAE=Treatment Emergent Adverse Event. Version 21.1 of MedDRA was used to code adverse events. Subjects reporting a particular adverse event (preferred term) more than once are counted once by preferred term and System Organ Class.
Related to study drug is defined as possibly, probably or definitely related to study drug.

研究中未出现与药物相关的ALT/AST异常

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根据器官系统分类的不良事件发生率

System Organ Class Preferred Term	TNP-2092 (N = 78) n (%)			Vancomycin (N = 39) n (%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Subjects with a least 1 TEAE						
Gastrointestinal disorders						
Nausea	6 (7.7)	6 (7.7)	0 (0.0)	1 (2.6)	1 (2.6)	0 (0.0)
Vomiting	5 (6.4)	1 (1.3)	0 (0.0)	2 (5.1)	0 (0.0)	0 (0.0)
Infections and infestations						
Cellulitis	2 (2.6)	5 (6.4)	0 (0.0)	2 (5.1)	3 (7.7)	0 (0.0)
Wound infection	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.1)	0 (0.0)

N=Number of subjects in the Safety Population. n=Number of subjects in the specific category; TEAE=Treatment Emergent Adverse Event. Version 21.1 of MedDRA was used to code adverse events.
Note: Percentages are calculated as 100 x (n/N).
Subjects reporting a particular adverse event (preferred term) more than once are counted once by preferred term and System Organ Class, and at the highest severity.

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总结

- TNP-2092 是一个多靶点偶联分子，通过抑制 RNA 聚合酶、DNA 旋转酶和拓扑异构酶IV三个靶点产生杀菌作用，具有较低的耐药频率，并对生物膜感染具有较强的杀菌活性
- 获得美国QIDP、快速通道和孤儿药资格认定
- 在120例ABSSSI患者参加的II期临床实验中，TNP-2092表现出良好的安全耐受性，治疗中不良事件发生率与万古霉素相当，均属轻度或中度，未出现SAE或死亡，未出现与药物相关的肝功能异常
- TNP-2092表现出良好的疗效，早期治疗应答率、治疗完成和随访治疗成功率均高于或等于万古霉素，其中包括由耐药菌株（MRSA和CRSA）感染的患者
- 在300mg q12h剂量下，TNP-2092在所有PK人群中达到或超过治疗医疗器械感染所需的系统暴露量，有望成为治疗医疗器械相关生物膜感染的全球首创产品

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第五届中国医药创新与投资大会

2020 CHINA BIOMED INNOVATION AND INVESTMENT CONFERENCE

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