THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Guo J, Chen X, Wu M, et al. Traditional Chinese medicine FYTF-919 (Zhongfeng Xingnao oral prescription) for the treatment of acute intracerebral haemorrhage: a multicentre, randomised, placebo-controlled, double-blind, clinical trial. *Lancet* 2024; published online Nov 12. https://doi.org/10.1016/S0140-6736(24)02261-X.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Guo J, Chen X, Wu M, et al. The traditional Chinese medicine FYTF-919 (Zhongfeng Xingnao oral prescription) for the treatment of acute intracerebral haemorrhage: a multicentre, randomised, placebo-controlled, double-blind, clinical trial

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1. List of CHAIN study group, trial investigators, and ethics committees

Trial Steering Committee (TSC)

Craig Anderson (Co-Chair, Co-Principal Investigator [PI]) at The Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, China; and The George Institute for Global Health, Sydney, Australia; The University of New South Wales; and the Neurology Department, Royal Prince Alfred Hospital.

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Xian Li, The George Institute for Global Health, China

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Ru Ban, Liaocheng People's Hospital, China
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Guangdong Provincial Hospital of Chinese Medicine: Project Management - Manli Wu, Dou Wang, Yanwen Zheng, Fengyan Huang, Zhixuan Ren, Jingbei Zhang, Zhihua Zheng, Kunhong Li, Xinwei Wang, Yongqi Li, Jiamin Cao, Lili Song, Huaying Zhu, Xinning Tan, Xinhong Qiu, Zhongkang Yang, Zhenzhen Lou, Tingting Xie, Haining Zhao, Yu Tang, Dafeng Hu, Wanzhen Cui, Mingjiang Xie, Daxiu Wang, Xiaoshu Wu, Yingyi Zheng, Rui Mao, Hao Chen, Min Luo,

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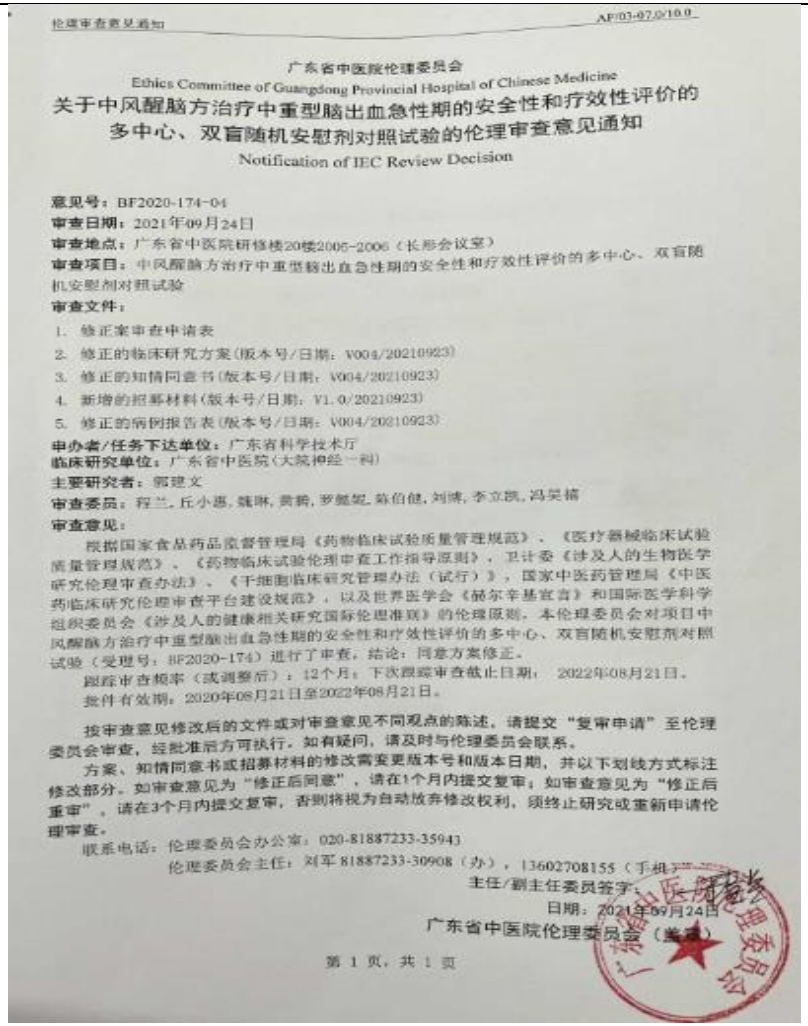
Ethics Committee approval

Central: Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China (Vice-chairperson Jun Liu). Approved protocol version 4.0 on 24 September 2021 (No. BF2020-174-04), used at Yuanhang Law Firm, Guangzhou; Yingke Law Firm, Guangzhou; People's sub-district office Guangzhou, China

Site: Liaoning Thrombus Treatment Centre of Integrated Chinese and Western Medicine, Shenyang; Linyi People's Hospital, Linyi; Liaocheng People’s Hospital, Liaocheng; Lianjiang People’s Hospital, Lianjiang; Traditional Chinese Medicine Hospital of Meishan, Meishan; Ganzhou People’s Hospital, Ganzhou; Panjin Central Hospital, Panjin; The First Affiliated Hospital of Shaoyang University, Shaoyang; Fushun Central Hospital, Fushun; People’s Hospital of Anshun City Guizhou Province, Anshun; The Affiliated Hospital of North Sichuan Medical College, Nanchong; The Affiliated Hospital of Xuzhou Medical University, Xuzhou; Chongqing Hospital of Traditional Chinese Medicine, Chongqing;The Third People’s Hospital of Hubei Province, Wuhan; The Fourth Affiliated Hospital of Guangzhou Medical University, Guangzhou; Guangdong Provincial Hospital of Chinese Medicine, Guangzhou; Guangdong Provincial Hospital of Chinese Medicine, Fangcun Hospital-Guangdong Provincial Hospital of Chinese Medicine, Guangzhou; Chongqing Hospital of The First Affiliated Hospital of Guangzhou University of Chinese Medicine (Chongqing Beibei Hospital of Traditional Chinese Medicine), Chongqing; The First Hospital of Lanzhou University, Lanzhou; Guangyuan Hospital of Traditional Chinese Medicine, Guangyuan; Guangdong Provincial Hospital of Chinese Medicine, Higher Education Mega Center Hospital- Guangdong Provincial Hospital of Chinese Medicine, Guangzhou; Inner Mongolia Hospital of Traditional Chinese Medicine, Hohhot; Traditional Chinese Medica Hospital of Xinjiang Uygur Autonomous Region, Urumqi; Ganzhou People's Hospital Neurology Department, Ganzhou; Guangdong Provincial Hospital of Chinese Medicine, Zhuhai Hospital-Guangdong Provincial Hospital of Chinese Medicine, Guangzhou; and Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu.

Central ethics committee approval document



伦理审查意见通知 AF/03-07.0/10.0

广东省中医院伦理委员会
Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine

关于中风醒脑方治疗中重型脑出血急性期的安全性和疗效性评价的多中心、双盲随机安慰剂对照试验的伦理审查意见通知

Notification of IEC Review Decision

意见号： BF2020-174-04
审查日期： 2021年09月24日
审查地点： 广东省中医院研修楼20楼2005-2006（长形会议室）
审查项目： 中风醒脑方治疗中重型脑出血急性期的安全性和疗效性评价的多中心、双盲随机安慰剂对照试验
审查文件：

1. 修正案审查申请表
2. 修正的临床研究方案（版本号/日期：V004/20210923）
3. 修正的知情同意书（版本号/日期：V004/20210923）
4. 新增的招募材料（版本号/日期：V1.0/20210923）
5. 修正的病例报告表（版本号/日期：V004/20210923）

申办者/任务下达单位： 广东省科学技术厅
临床研究单位： 广东省中医院（大院神经一科）
主要研究者： 郭建文
审查委员： 程兰、丘小惠、魏琳、黄腾、罗懿妮、陈伯健、刘博、李立凯、冯昊禧
审查意见：

根据国家食品药品监督管理局《药物临床试验质量管理规范》、《医疗器械临床试验质量管理规范》、《药物临床试验伦理审查工作指导原则》，卫计委《涉及人的生物医学研究伦理审查办法》、《干细胞临床研究管理办法（试行）》，国家中医药管理局《中医药临床研究伦理审查平台建设规范》，以及世界医学会《赫尔辛基宣言》和国际医学科学组织委员会《涉及人的健康相关研究国际伦理准则》的伦理原则，本伦理委员会对项目中风醒脑方治疗中重型脑出血急性期的安全性和疗效性评价的多中心、双盲随机安慰剂对照试验（受理号：BF2020-174）进行了审查，结论：同意方案修正。

跟踪审查频率（或调整后）：12个月；下次跟踪审查截止日期：2022年08月21日。

批件有效期：2020年08月21日至2022年08月21日。

按审查意见修改后的文件或对审查意见不同观点的陈述，请提交“复审申请”至伦理委员会审查，经批准后方可执行。如有疑问，请及时与伦理委员会联系。

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联系电话：伦理委员会办公室：020-81887233-35943
伦理委员会主任：刘军 81887233-30908（办），13602708155（手机）

主任/副主任委员签字：
日期：2021年09月24日
广东省中医院伦理委员会（盖章）

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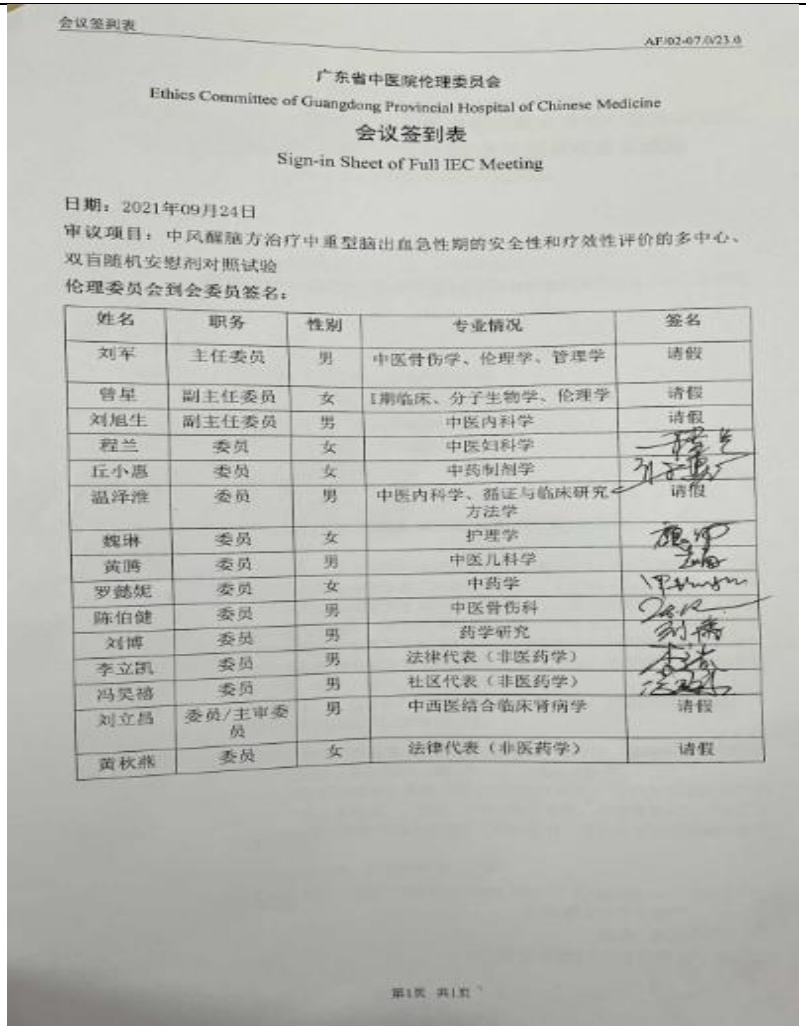

会议签到表 AF/02-07.0/23.0

广东省中医院伦理委员会
Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine

会议签到表
Sign-in Sheet of Full IEC Meeting

日期： 2021年09月24日
审议项目： 中风醒脑方治疗中重型脑出血急性期的安全性和疗效性评价的多中心、双盲随机安慰剂对照试验
伦理委员会到会委员签名：

姓名	职务	性别	专业情况	签名
刘军	主任委员	男	中医骨伤学、伦理学、管理学	请假
管星	副主任委员	女	肝病临床、分子生物学、伦理学	请假
刘旭生	副主任委员	男	中医内科学	请假
程兰	委员	女	中医妇科学	
丘小惠	委员	女	中药制剂学	
温泽淮	委员	男	中医内科学、循证与临床研究方法学	请假
魏琳	委员	女	护理学	
黄腾	委员	男	中医儿科学	
罗懿妮	委员	女	中药学	
陈伯健	委员	男	中医骨伤科	
刘博	委员	男	药学研究	
李立凯	委员	男	法律代表（非医药学）	
冯昊禧	委员	男	社区代表（非医药学）	
刘立昌	委员/主审委员	男	中西医结合临床肾病学	请假
黄秋燕	委员	女	法律代表（非医药学）	请假

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2. Timelines, meetings, and modifications to the protocol

Date	Name of document / event	Brief summary of changes / notes
8 May 2021	CHAIN Protocol V1.0	Original
17 May 2021	Steering Committee Meeting 1st	Kick-off meeting Review of the first draft of protocol
7 June 2021	CHAIN Protocol V1.1 Amendment 1	Adding previous clinical trials and underlying mechanisms of Chinese herbal medicine for ICH treatment.
26 June 2021	CHAIN Protocol V2.0 Amendment 2	Inclusion criteria for item 1) changed from "Age ≥18 years and Age <90 years" to "Age ≥18 years"; Added health economic evaluation.
14 July 2021	CHAIN Protocol V3.0 Amendment 3	Revision of "heavy burden of ICH" in the background section and "sample size calculation" Inclusion criteria for item 3) changed from "Presentation within 24 hours of symptom onset (or last seen well)" to "Presentation within 48 hours of symptom onset (or last seen well)"; Time to initiation of intervention changed from '6 hours after randomisation' to 'the intervention after the randomisation should be performed as soon as possible'.
23 September 2021	CHAIN Protocol V4.0 Amendment 4	Inclusion criteria for item 3) changed from "Presentation within 24 hours of symptom onset (or last seen well)" to "Presentation within 48 hours of symptom onset (or last seen well)"; Updated inclusion criteria for item 4) Meet any of the following criteria: a) NIHSS ≥8, or b) GCS 7-14; Added 'secondary to antiplatelet treatment' into the exclusion criteria; Added the UW-mRS scores at 180 days as secondary outcome; Added the Barthel Index at 28 days, 90 days, and 180 days as secondary outcomes; Added the mRS/ EQ-5D/5L at 28 days and 180 days as secondary outcomes; Kept the follow up at the onset of SAP, 3 days and 7 days after the occurrence of SAP and deleted "at 14 days"; Kept three stratification factors, including site, neurological severity (NIHSS <15 vs≥15), and haematoma location (basal ganglia + lobe vs thalamus + cerebellum + brain stem + ventricle); Updated the randomisation to 'double-blinded randomisation will commence within 48 hours'; Added "the intervention after the randomisation should be performed as soon as possible" for the time to initiation of Chinese herbal medicine FYTF-919 or placebo; Estimated sample size changed from 1500 to 1504; Clarified the assessment time for key outcomes: changed from "XXX days after the occurrence of ICH" into "XXX days after starting the treatment";

		Added the number of clinical trial registration for CHAIN study “NCT05066620”.
24 September 2021	DSMB Meeting 1st	Kick-off meeting Protocol overview DSMB charter review and finalisation DSMB mock table review
24 November 2021	Recruitment	First participant randomised at Guangdong Provincial Hospital of Chinese Medicine, China
1 November 2022	DSMB Meeting 2nd	DSMB reviewed available data and had no concerns for the safety of participants Further meeting in line with the schedule in the charter
19 April 2023	DSMB Meeting 3rd	Reviewed both blinded and unblinded reports and recommended the trial continue as planned.
26 September 2023	DSMB Meeting 4th	Reviewed both blinded and unblinded reports, and interim analysis report DSMB recommended the trial continue as planned
28 December 2023	Recruitment completed	Last patient recruited into study
02 April 2024	Patient follow-up	Last 90-day outcome assessment for participants
17 April 2024	Data lock	
26 April 2024	Unblinding of data to key members of Steering Committee	

3. The CONSORT 2010 checklist of information to include when reporting a randomised trial

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]
Introduction			
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Methods			
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Results

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Discussion

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			[illegible]

Other information

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[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

4. Agencies providing funding for the study

This study received funding from the following grants in China: Key-Area Research and Development Program of Guangdong Province (No.2020B1111100009), Guangzhou Municipal Science and Technology Bureau (No.SL2023B01J00017); Guangdong Provincial Key Laboratory of Research on Emergency in TCM (2023B1212060062). Craig Anderson is supported to undertake stroke research by grants from the National Health and Medical Research Council (NHMRC) of Australia (APP1149987).

5. Screening procedures

Investigators at participating hospital sites were required to fill in a screening log for all potentially eligible patients with acute intracerebral haemorrhage (ICH) confirmed by brain imaging. Patients who failed to be randomised would have the reason recorded as a screening failure. The patients who met the screening criteria would be entered with the stratification factors into the randomised system and be assigned a random number and drug number.

6. Inclusion/exclusion criteria

Inclusion criteria: Patients must meet all following criteria:

- Age ≥18 years
- Diagnosis of spontaneous ICH, confirmed by brain imaging
- Presentation within 48 hours of symptom onset (or last seen well)
- Meet any of the following criteria: a) NIHSS score ≥8, or b) GCS score ≤14
- Provide written informed consent by patient (or approved surrogate)

Exclusion criteria: Patients will NOT be eligible if there is one or more of the following:

- ICH secondary to a structural abnormality in the brain (e.g. cerebrovascular malformation, arterial aneurysm, tumour, Moyamoya disease, trauma, or previous ischaemic stroke), or secondary to cerebral amyloid angiopathy, or secondary to reperfusion treatment for ischaemic stroke, or secondary to anticoagulant treatment, or secondary to antiplatelet treatment
- Unlikely to potentially benefit from therapy (e.g. advanced dementia) or judged by responsible treating clinician to have a high likelihood of early death irrespective of treatment
- Other medical illness that will interfere with outcome assessments and follow-up (e.g. known significant pre-stroke disability [modified Rankin scale {mRS} scores 3-5], advanced cancer and severe renal failure)
- Known definite contraindication to the Chinese herbal medicine
- Women who are known to be pregnant or lactating
- Currently participating in another trial which would interfere with outcome assessments

7. Treatment drug and placebo

7.1 Active agent

Name of treatment drug: FYTF-919 (Zhong Feng Xing Nao [ZFXN] prescription)

Ingredients: FYTF-919 comprises four Chinese herbs – Renshen (Panax ginseng), Dahuang (Radix et Rhizoma Rhei), Sanqi (Radix Notoginseng), and Chuanxiong (Rhizoma Ligustici Chuanxiong), with sorbic acid and polysorbate 80 as auxiliary materials. The compounds in FYTF-919 were identified by information regarding molecular formula, molecular weight, peak time and secondary fragment ions with reference substances, from databases and related literatures. A total of 30 components were identified or tentatively identified (**Table 7.1**), including 15 triterpenoid saponins (ginsenosides), 9 organic acids and 6 anthraquinones. The representative compounds contained Ginsenoside Re, Ginsenoside Rg1, Ginsenoside Rb1, Notoginsenoside R1, Emodin-8-O-β-D-glucoside, Aloe-emodin, Rhein, Emodin and Ferulic Acid, and other constituents.

Quality control and stability assessment: An ultra-high performance liquid chromatography coupled with Q Exactive hybrid quadrupole-Orbitrap mass spectrometry (UHPLC-Q Exactive-Orbitrap MS) system was employed to assess the quality and stability of the drug. A total of 30 chemical profiles were detected in different batches of FYTF-919 and the similarity between different batches exceeded 0.95 (**Fig 7.1**). Similarity analysis for fingerprints of the three batches are provided in **Table 7.2**. The relative standard deviations (RSDs %) of 10 representative compounds, including notoginsenoside R1, ginsenoside Re, ginsenoside Rg1, ginsenoside Rb1, ginsenoside Rd, ferulic acid, emodin-8-O-glucoside, aloe-emodin, rhein and emodin, were all below 15%, as outlined in **Table 7.3**.

Dose and usage: The study medication was prepared as a brown-yellow liquid specifically in a 100 ml per bottle (**Fig 7.2**). The method and frequency of delivery in patients is determined by their level of consciousness and ability to swallow. Patients who are awake and have a normal swallow, take warm FYTF-919 orally, at a dose of 33 ml from 30 min after a meal. For patients with swallowing dysfunction, insufficient oral intake, unconsciousness, or are in a critical condition, a dose of 25 ml every 6 h is usually given via a nasogastric tube. For this study, patients were to take FYTF-919 immediately after randomisation and until 28 days.

Manufacturer: FYTF-919 was manufactoured at the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine.

Table 7.1 Compounds identified in FYTF-919

No.	T_R/min	$[M-H]^-$/[M-HCOO]$^-$	Fragment ion (MS^2)	Formula	Identification compound
1	1.78	169.0132	125.02	$C_7H_6O_5$	Gallic acid *
2	3.73	353.0878	191.06, 179.03, 134.04	$C_{16}H_{18}O_9$	Neochlorogenic acid *
3	7.45	353.0881	191.06	$C_{16}H_{18}O_9$	Chlorogenic acid *
4	8.72	353.0879	173.04, 179.03, 191.06, 135.04	$C_{16}H_{18}O_9$	Cryptochlorogenic acid *
5	9.56	515.1185	179.03, 191.05, 353.09, 135.04, 335.07	$C_{25}H_{24}O_{12}$	Isochlorogenic acid C (4,5)
6	10.29	515.1192	173.04, 179.03, 191.05, 353.09, 135.04	$C_{25}H_{24}O_{12}$	Isochlorogenic acid B
7	10.30	193.0498	134.04, 178.03, 149.06, 137.02	$C_{10}H_{10}O_4$	Ferulic acid *
8	10.38	515.1193	191.06, 179.03, 135.04	$C_{25}H_{24}O_{12}$	Isochlorogenic acid A
9	10.45	977.5324	931.53, 799.48, 637.43, 475.38	$C_{47}H_{80}O_{18}$	Notoginsenoside R_1*
10	10.54	515.1190	173.04, 179.03, 191.05, 135.04	$C_{25}H_{24}O_{12}$	Isochlorogenic acid C
11	10.64	991.5484	945.54, 799.48, 783.49, 637.43, 475.38, 765.48, 619.42, 391.29	$C_{48}H_{82}O_{18}$	Ginsenoside Re *
12	10.70	845.4899	637.43, 799.48, 475.38, 619.42	$C_{42}H_{72}O_{14}$	Ginsenoside Rg_1*
13	12.39	431.0989	269.05, 240.04, 225.04	$C_{21}H_{20}O_{10}$	Emodin-8-O-β-D-glucoside *
14	14.08	845.4905	799.48, 475.38, 637.43, 391.29	$C_{42}H_{72}O_{14}$	Ginsenoside Rf
15	14.30	845.4904	799.48, 323.10, 475.38, 637.43	$C_{42}H_{72}O_{14}$	Pseudoginsenoside F_{11}
16	14.74	445.1143	283.06, 240.04	$C_{22}H_{22}O_{10}$	Physcion-8-O-β-D-glucoside *

17	16.66	829.4959	783.49, 637.43, 475.38, 391.28, 619.42, 459.35	$C_{42}H_{72}O_{13}$	Ginsenoside F_2
18	17.29	829.4958	783.49, 475.38, 637.43, 391.29, 619.42	$C_{42}H_{72}O_{13}$	Ginsenoside Rg_2
19	17.44	1153.6000	1107.59, 945.54, 783.49, 621.44, 459.38	$C_{54}H_{92}O_{23}$	Ginsenoside Rb_1*
20	19.50	955.4908	793.47, 569.38, 523.38, 613.37	$C_{48}H_{76}O_{19}$	Ginsenoside Ro
21	19.72	1123.5903	1077.58, 945.54, 783.49, 621.44, 459.38, 375.29	$C_{53}H_{90}O_{22}$	Ginsenoside Rc
22	21.44	269.0444	253.05, 240.04	$C_{15}H_{10}O_5$	Aloe-emodin *
23	22.71	1123.5903	1077.58, 945.54, 783.49, 621.43, 459.38	$C_{53}H_{90}O_{22}$	Ginsenoside Rb2
24	23.52	1123.5903	1077.58, 945.54, 783.49, 621.44, 459.38, 375.29	$C_{53}H_{90}O_{22}$	Ginsenoside Rb3
25	24.05	283.0259	257.05, 239.03	$C_{15}H_8O_6$	Rhein *
26	24.26	991.5485	945.54, 783.49, 621.44, 459.38, 765.48	$C_{48}H_{82}O_{18}$	Ginsenoside Rd*
27	30.50	269.0441	225.05	$C_{15}H_{10}O_5$	Emodin *
28	30.42	829.4959	783.49, 621.44, 459.38	$C_{42}H_{72}O_{13}$	(*S*)-Ginsenoside Rg_3
29	30.67	829.4959	783.49, 621.44, 459.38	$C_{42}H_{72}O_{13}$	(*R*)-Ginsenoside Rg_3
30	32.27	253.0502	225.05	$C_{15}H_{10}O_4$	Chrysophanol *

* Compared to reference substances

Figure 7.1 MS chromatographic fingerprints for three batches of FYTF-919

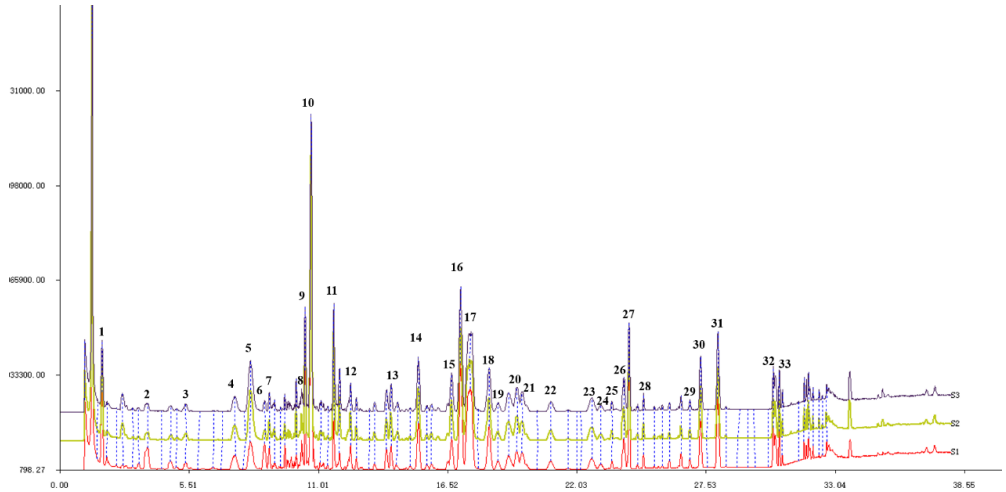


Table 7.2 Similarity analysis for fingerprints of the three batches

	S1	S2	S3
S1	1	0.984	0.978
S2	0.984	1	0.98
S3	0.978	0.98	1

Table 7.3 Similarity analysis for 10 representative compounds from 3 batches of FYTF-919

Compounds	C(μg/mL)				
	No. 202109.6	No. 20211208	No. 20220419	Mean±SD	RSD%*
Notoginsenoside R1	2135.65 ± 27.14	2459.68 ± 61.83	2379.76 ± 32.62	2325.03 ± 168.81	7.26
Ginsenoside Re	1102.94 ± 19.83	1380.48 ± 19.48	1360.30 ± 31.04	1281.24 ± 154.74	12.08
Ginsenoside Rg_1	7338.03 ± 139.94	9269.25 ± 250.37	9081.81 ± 271.27	8563.03 ± 1065.01	12.44
Ginsenoside Rb_1	7801.56 ± 61.02	9300.57 ± 91.54	9096.19 ± 47.17	8732.77 ± 812.90	9.31
Ginsenoside Rd	1665.45 ± 12.37	2146.67 ± 15.97	2088.02 ± 7.41	1966.71 ± 262.54	13.35
ferulic acid	103.84 ± 2.11	86.72 ± 0.56	79.64 ± 1.66	90.07 ± 12.44	13.81
aloe-emodin	6.07 ± 0.1	7.21 ± 0.04	7.04 ± 0.12	6.77 ± 0.62	9.08
rhein	29.95 ± 0.66	33.95 ± 0.18	33.05 ± 0.54	32.32 ± 2.10	6.49
emodin	8.17 ± 0.38	9.47 ± 0.26	9.39 ± 0.5	9.01 ± 0.73	8.09
emodin-8-O-glucoside	28.35±0.33	33.43±0.24	33.08±0.88	31.60 ± 2.87	9.07

*Relative standard deviation

7.2 Placebo

Manufacturer: The placebo was developed and manufactured by Guangdong Huixiangyuan Biotechnology Co., Ltd. Invention patents based on placebos were published by the State Intellectual Property Office of China (application number 202211384394.6).

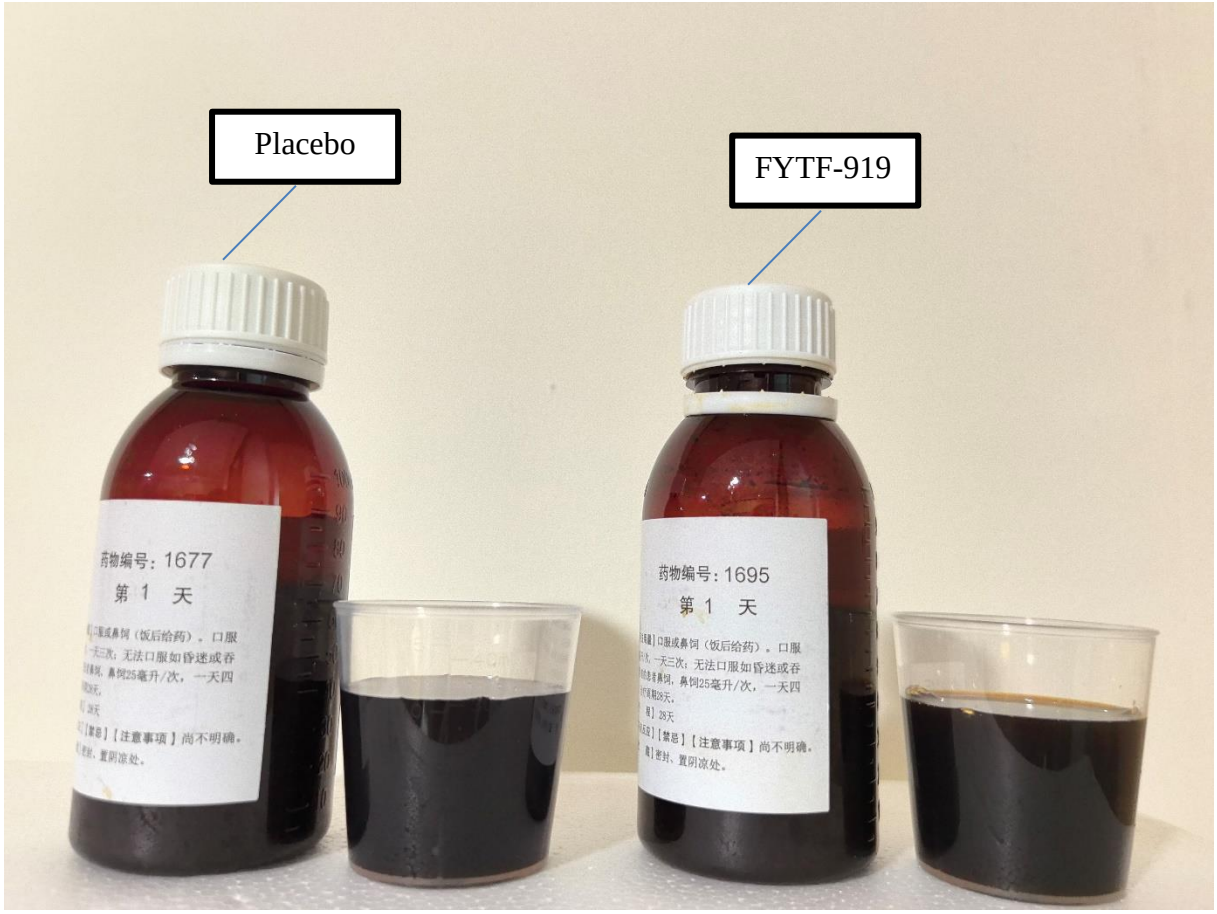
Features: The appearance and internal laws of flavour level structure, colour and gloss, texture, basic flavour, main flavour, and volatile aroma of FYTF-919 were imitated in the placebo, which was composed of food-grade and medicinal-valueless materials, such as soy protein

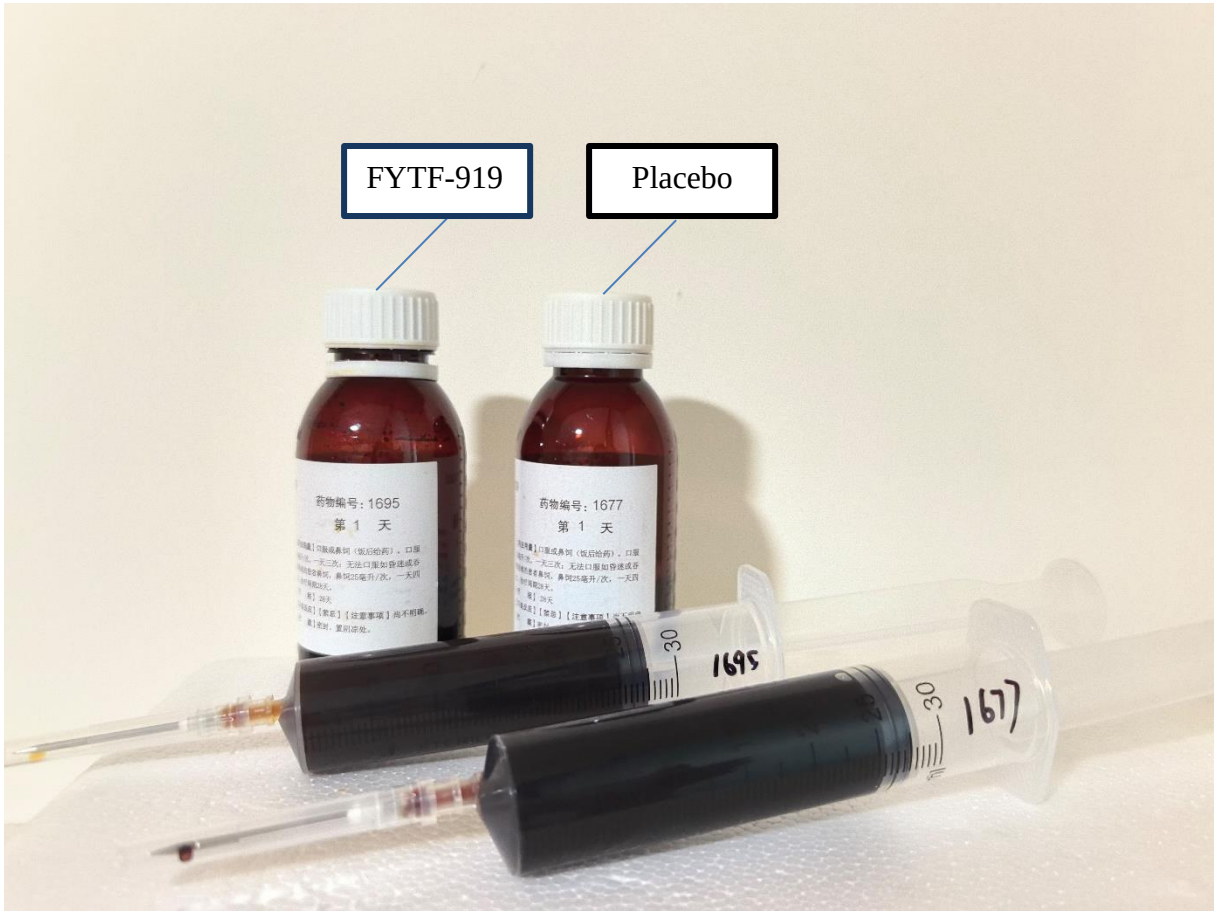
powder, vital wheat gluten, and brown sugar syrup, as outlined in **Table 7.4**. The appearances of active drug and placebo are shown in **Fig 7.2**.

Table 7.4 Features of FYTF-919 and imitated ingredients of placebo.

Items	Features of FYTF-919	Imitated ingredients of placebo
Colour and gloss	Dark black	Dark black
Texture	Slightly viscous	Maltodextrin
	Homogeneous	Vital wheat gluten
Basic flavour	Sweet	Brown sugar syrup, stevioside
	Bitter	Soy protein powder
	Sour	DL-malic acid
Main flavour	Neem wood	Food essence
Volatile aroma	Aroma of rotting wood	Food essence
	Earthy smell	Soy protein powder, maltodextrin

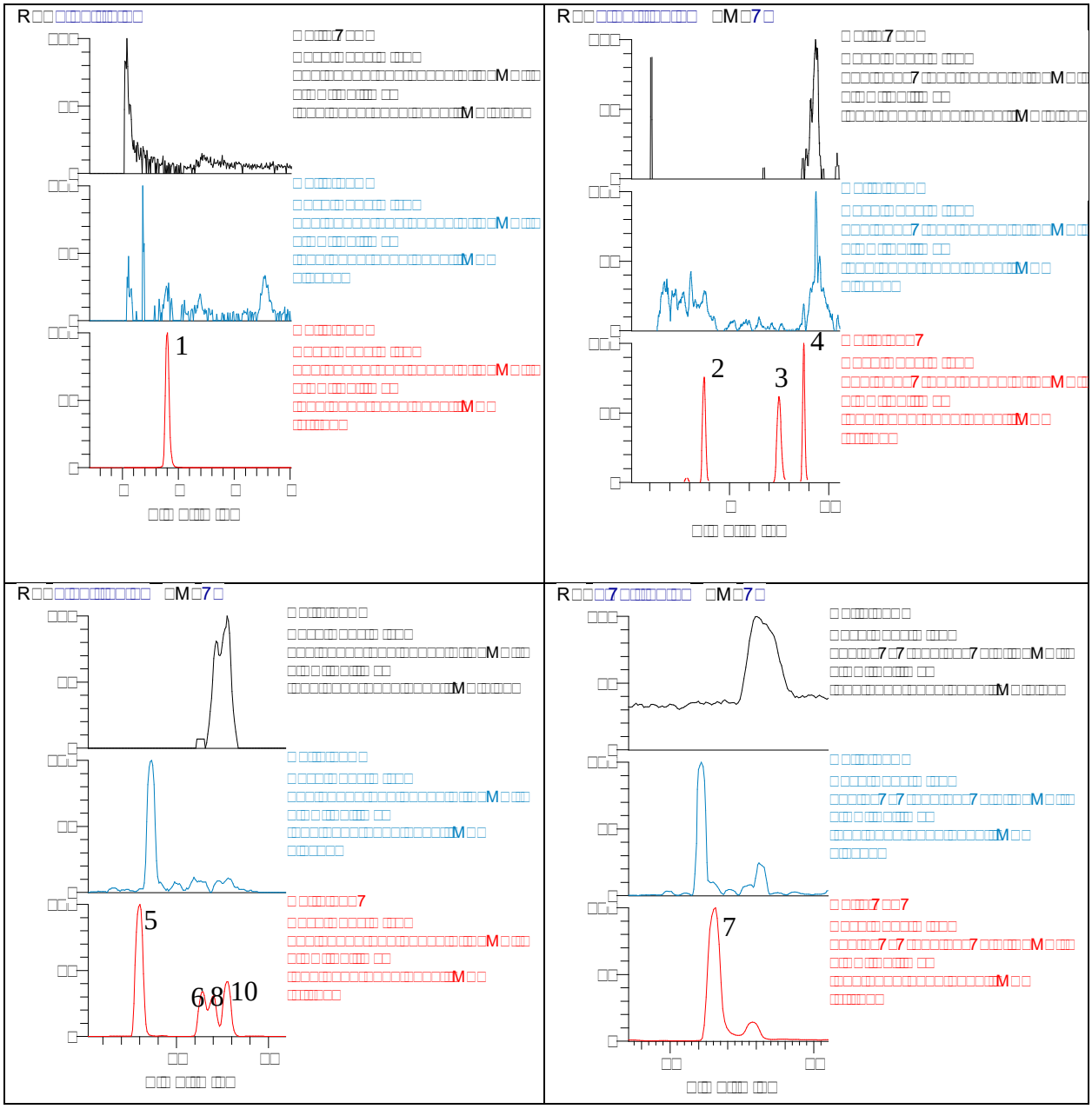
Fig 7.2 Pictures for FYTF-919 and placebo

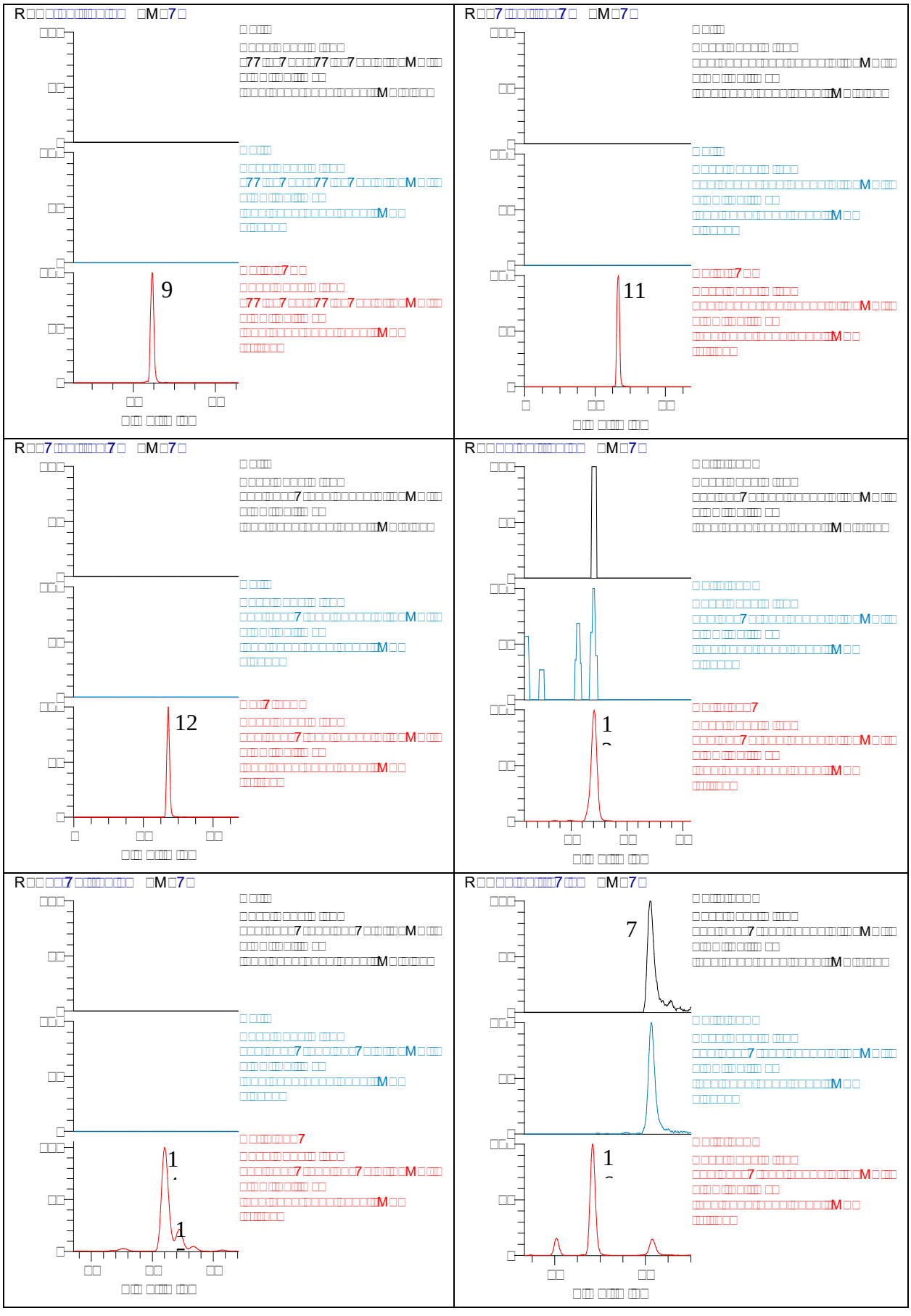


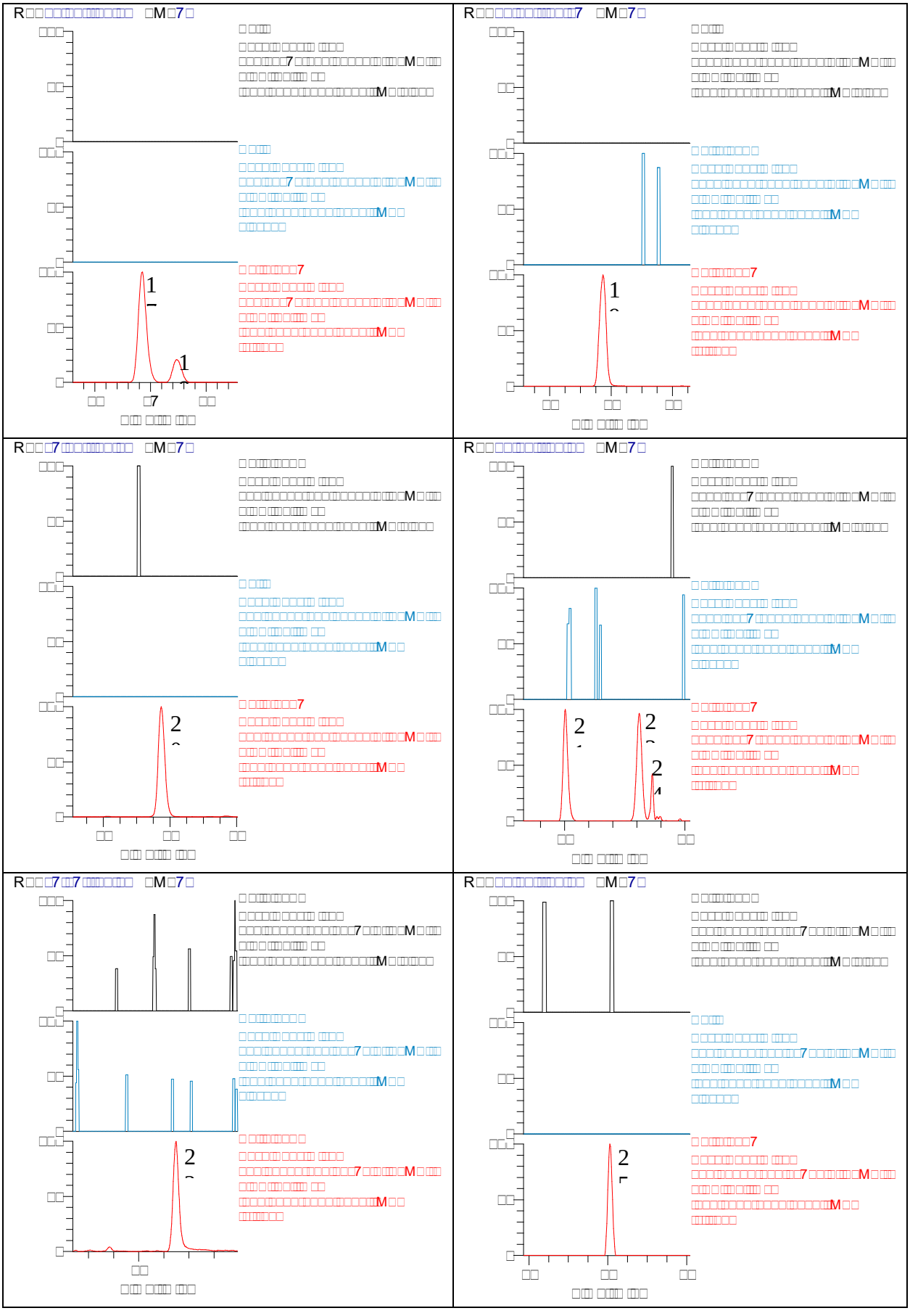


The representative compounds of FYTF-919 were virtually absent in the placebo group, as shown in **Fig. 7.3**. The compounds tested in (B) depend on the herbs contained in FYTF-919, of which Notoginsenoside R1, Ginsenoside Re, Ginsenoside Rg1, and Ginsenoside Rb1 were attributed to Panax ginseng and Radix Notoginseng; Ferulic acid was attributed to Rhizoma Ligustici Chuanxiong, Emodin, Aloe-emodin, and Rhein;and Emodin-8-O-β-D glucoside was attributed to Radix et Rhizoma Rhei. In comparison with the standard ion chromatograms of graph (B), graph (C) appears to have the same exacted ion peak as well as peak retention time, and exhibits high ion intensity. Conversely, graph (D) shows no matching exacted ion peak and peak retention time as shown in graph (B) and has lower ion intensity. These results indicate that FYTF-919 represented by graph (C) contains the above 8 compounds, while the placebo represented by graph (D) does not contain any of the 8 compounds.

Figure7.3. Extracted ion chromatograms for blank, placebo and FYTF-919 sssamples. (Black: blank solution; Blue: placebo; Red: FYTF-919; D:)




9
11
12
1
7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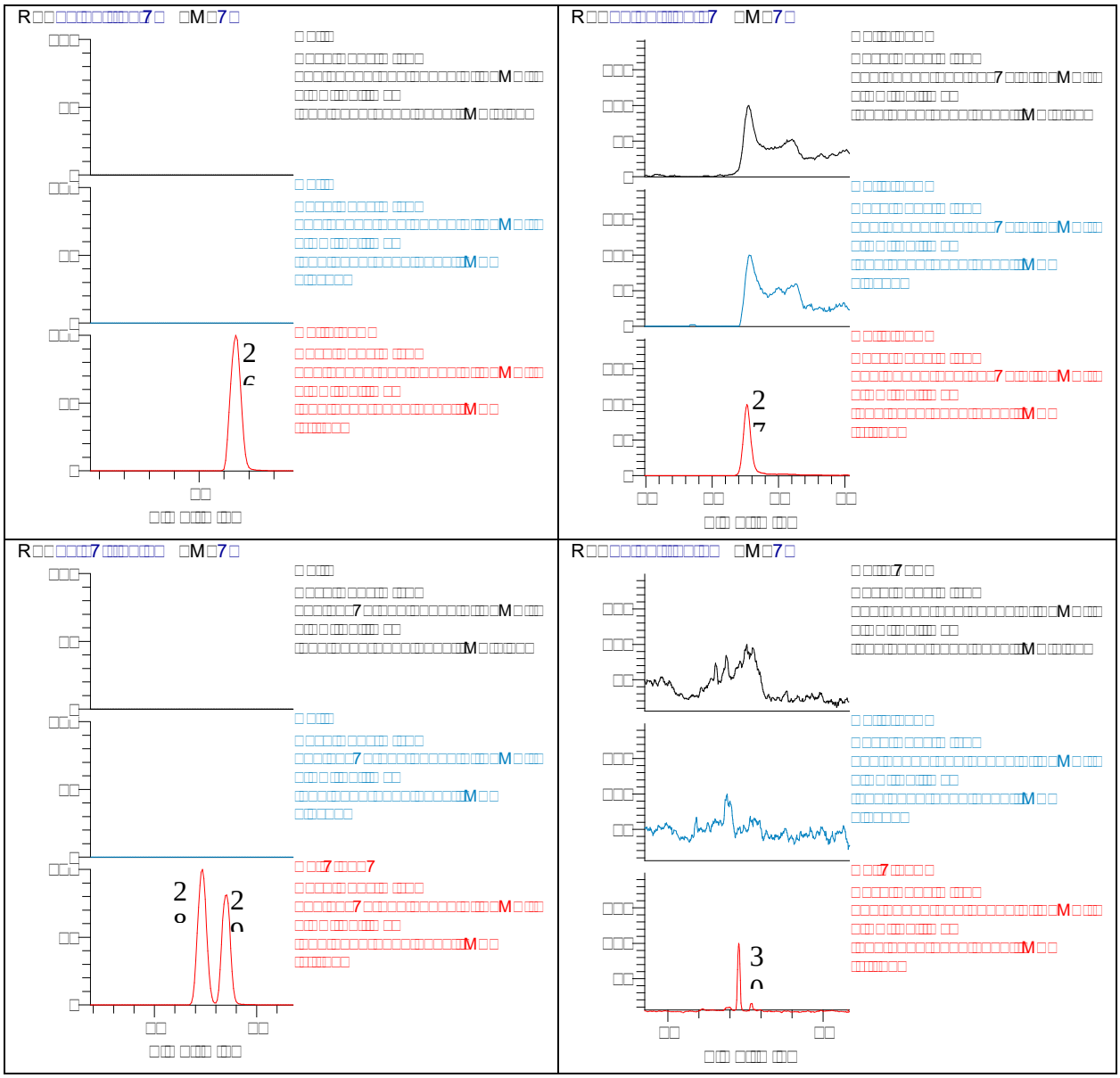

7.3 Comparison between treatment drug and placebo

We designed and conducted a small sample, randomised double-blind study to assess the effectiveness of the blinding of the study medication, and the physical similarity of the placebo of raw food material compared with FYTF-919 that were used in the study. The evaluation indicators of placebo effect include consistency evaluation and simulation of the actual situation in clinical trials. The test drug and placebo were blinded, and multiple evaluators were invited to evaluate the appearance, smell, sweetness, bitterness, and overall taste of the blinded trial drug and placebo simultaneously.

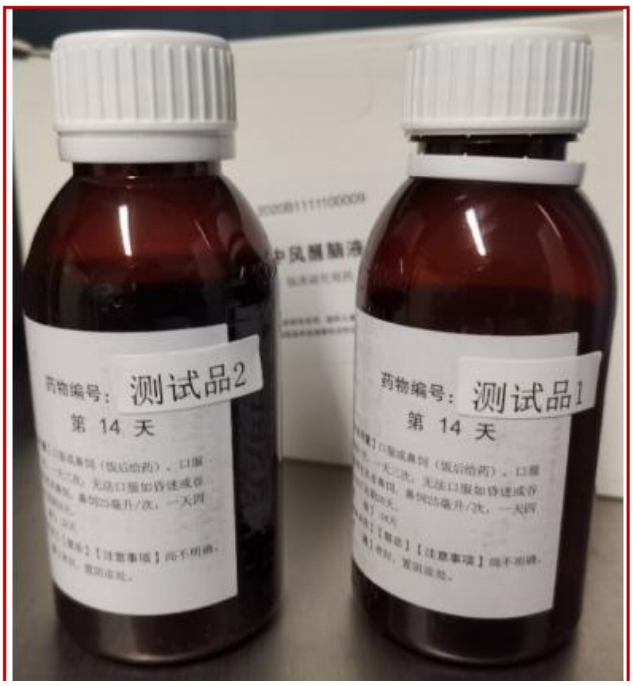

Figure 7.4. Sample 1 was test FYTF-919 drug, sample 2 was placebo.

Consistency test between placebo and trial drug. Researchers blinded the trial drug and the evaluators assessed the blinded trial drug and placebo, including the appearance and taste of the liquid. The results are shown in Tables 7.5-7.6 below:

Table 7.5. Assessment of conformity between FYTF-919 and p**lacebo on appearance**

Evaluation content	Result, n (%)				
	Completely consistent	Relatively consistent	Half of each	Relatively inconsistent	Inconsistent
Liquid color	6 (60%)	4 (40%)	0 (0%)	0 (0%)	0 (0%)
Clarity	7 (70%)	3 (30%)	0 (0%)	0 (0%)	0 (0%)

Table 7.6. Assessment of conformity between FYTF-919 and placebo on taste

Evaluation content	Result, n (%)				
	Completely consistent	Relatively consistent	Half of each	Relatively inconsistent	Inconsistent
Smell	0 (0%)	3 (30%)	2 (20%)	0 (0%)	5 (50%)
Sweetness	1 (10%)	1 (10%)	0 (0%)	4 (40%)	4 (40%)
Bitterness	0 (0%)	1 (10%)	1 (10%)	2 (20%)	6 (60%)
Overall taste	1 (10%)	1 (10%)	1 (10%)	4 (40%)	3 (30%)

Actual situation of the simulation experiment. There were 14 clear plastic cups prepared, 7 of which were filled with FYTF-919 and 7 with placebo. A syringe was used to ensure an equal amount of FYTF-919 and placebo were poured into each cup. Participants were allowed to choose the selection of cups for tasting. They were asked whether the cup contained the test drug or placebo. The results in Table 7.7 show that participants were able to correctly distinguish the placebo with an accuracy of 0% (0 vs 7).

Table 7.7.The test results of the simulation experiment

Evaluation content	Correct	Incorrect	Indistinct	Sum up
FYTF-919	6	0	1	7
Placebo	0	5	2	7

As tested by reviewers, FYTF-919 and placebo were relatively consistent in colour and clarity. In terms of taste, there was a discrepancy between sweetness, aroma, and overall taste, but the bitterness was relatively consistent. The placebo tasted slightly sweet, while FYTF-919 tasted slightly bitter; and FYTF-919 hasda stronger fragrant taste. When the evaluator independently tasted the drug, the evaluator of the test drug was generally able to confirm that it was the test drug, while the evaluator could not adequately distinguish it from the placebo. The conclusion was that the placebo-making method was successful.

8. Training of investigators

All CHAIN investigators were trained in the protocol, Good Clinical Practice (GCP) procedures, and use of the National Institute for Health Stroke Scale (NIHSS), modified Rankin scale (mRS) and EQ-5D-5L, if they had no recent certification. Drs Yingfeng Wan and Tingting Xie recieved training and were on-line certified in use of mRS and NIHSS. They provided training and certification to any site assessor who had not received similar online training and certification. All such assessors received mRS training via in-person meetings or on-line during the study period. After each training session, the assessors receive an examination ensure that he/she was suitably qualified. Details of the content, frequency and evaluation of assessors are available upon request.

9. Schedule for monitoring of sites

Project management team undertook quality control activities necessary for the conduct of the trial in accordance with the protocol, applicable guidelines, and regulations. The first monitoring visit was within 1 week after the site had randomised the first patient following initiation and activation of the site. The second monitoring visit took place after every 10-20 patients had been randomised at each site or every 3 months. Subsequent monitoring visits were arranged every 6 months, and the frequency of monitoring can be adjusted appropriately according to the recruitment of subjects in sites, the collection of original data, the input of EDC, the progress of questioning and answering, and the problems found in the monitoring process.

All sites were monitored at least twice per year. Any significant deviation from the planned monitoring timelines was explained and documented in the monitoring visit report, and the monitoring plan was amended if appropriate.

The monitoring visit served to obtain 100% source data verification of the following data for all randomised patients: patient consent forms (patient consent forms were reviewed for compliance with GCP/ICH GCP); patient existence; inclusion & exclusion criteria; all outcome data; treatment allocation; and all serious adverse event forms to source verification.

The project manager selected 30% key sites to conduct co-monitoring visits according to the needs, found the risks in the process of the trial, corrected them in time, and controlled the quality of the data.

The CHAIN study was affected by the COVID-19 pandemic. Because of the requirement for epidemic prevention policies to be enacted in many participating hospitals, project staff were unable to undertake monitoring activities directly at sites during certain months in 2021 and 2022. To ensure integrity and authenticity of key data, the project team with data management undertook risk-based monitoring of the data on the participants. The sponsor assigned multiple regional coordination locations to manage recruitment and data collection at the centre. After on-site monitoring was allowed in 2022, the CRAs verified all data that required source data verification.

At the end of the study, 26 sites had received at least 50 on-site monitoring visits.

10. Definitions of protocol violations and deviations

Protocol deviation / violations were any unapproved changes, or departures from the study design or procedures of the CHAIN protocol, that were under the investigator's control and had not been reviewed and approved by the Central Coordinating Centre (CCC) or IRB/EC. Protocol deviation / violations had two categories: 'major (reportable) violations', and 'minor (non-reportable) violations' which were also called 'Protocol Deviations'.

Major (reportable) protocol violations

Major protocol violations were any unapproved changes in the research study design and/or procedures that were within the investigator's control, and not in accordance with the approved protocol, that may have affected the participant's rights, safety or well-being, or the completeness, accuracy, and reliability of the study data. All major violations were required to be reported to the IRB/EC, regulatory authority and/or sponsor, in keeping with relevant national guidance and conforming to national timelines for reporting. The CCC criteria for defining major violations included any of the following violation events:

- There was harm, or posed a significant or substantive risk of harm, to the participant;
- It had resulted in a change to the participant's clinical or emotional condition or status;
- There was damage to the scientific completeness or soundness of the study data;
- There was evidence of willful or knowing misconduct on the part of the investigator(s);
- There was serious or continuing noncompliance with federal, state, or local regulations.

Examples of major protocol violations included, but were not limited to:

a) enrolment of a participant who did not meet the eligibility criteria;

b) failure to obtain informed consent prior to any study-specific tests/procedures;

c) failure to follow protocol procedures that specifically related to intervention and the primary safety or efficacy endpoints of the study;

d) failure to follow study medication management requirements;

e) failure to follow randomisation, blinding and unblinding procedures.

Minor (non-reportable) protocol violations (also called protocol deviations)

Minor protocol violations were any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the approved protocol that do not have a major impact on either the participant's rights, safety or well-being, or the completeness, accuracy, and reliability of the study data. Minor protocol violations were not necessarily reportable to the IRB/EC. CCC criteria for minor violations and included all of the following:

- the violation did not harm or pose a significant risk of substantive harm to the research participant, and
- the violation did not result in a change to the participant's clinical or emotional condition or status, and

- the violation did not damage the completeness, accuracy, and reliability of the data collected for the study, and
- the violation did not result from willful or knowing misconduct on the part of the investigator(s), and
- the violation did not involve serious or continuing noncompliance with federal, state, or local regulations.

Examples of minor protocol violations included, but are not limited to:

a) patient being unable to complete the self-administered quality of life questionnaire when they were capable of doing so;
b) follow-up visits / assessments performed outside of defined time points or window.

Participant took a contraindicated Traditional Chinese Medicine

- If 1 overlapping component of FYTF-919 was used for <14 days or 2 overlapping components were used for <7 days, it is considered a minor PV.
- If 1 overlapping component of FYTF-919 was used ≥14 days or 2 overlapping components were used ≥7 days (including 7 days), it is considered a major PV.

11. Complete list of protocol violations identified through monitoring*

Code	Major / Minor	Description 1	Description 2	FYTF-919	Placebo	Total
1	Major	Consent form	Signed the wrongly version of Consent Form, but re-signed the new version.	27/817 (3.30%)	28/831 (3.37%)	55
2.1	Major	Inclusion criteria	Not me Inclusion Criteria 2: Presentation over 48 hours of symptom onset (or last seen well).	4/817 (0.49%)	4/831 (0.48%)	8
2.2	Major	Exclusion criteria	Satisfy Exclusion Criteria **1**: ICH secondary to a structural abnormality in the brain (e.g. cerebrovascular malformation, arterial aneurysm, tumour, Moyamoya disease, trauma, or previous ischaemic stroke), or secondary to cerebral amyloid angiopathy, or secondary to reperfusion treatment for ischaemic stroke, or secondary to anticoagulant treatment, or secondary to antiplatelet treatment.	2/817 (0.24%)	4/831 (0.48%)	6
2.2	Major	Exclusion criteria	Satisfy Exclusion Criteria **2**: Unlikely to potentially benefit from therapy (e.g. advanced dementia) or judged by responsible treating clinician to have a high likelihood of early death irrespective of treatment.	2/817 (0.24%)	6/831 (0.72%)	8
2.2	Major	Exclusion criteria	Satisfy Exclusion Criteria **3**: Other medical illness that will interfere with outcome assessments and follow-up (e.g. known significant pre-stroke disability [modified Rankin scale {mRS} scores 3-5], advanced cancer and severe renal failure).	5/817 (0.61%)	4/831 (0.48%)	9
5	Minor	Medication management	The medication was stored over the temperature requirement, but the quality was not affected.	0/817 (0.00%)	4/831 (0.48%)	4
5	Major	Medication management	Patients were dispensed medication from other sites of the same city due to 1) insufficient stock in sites; 2) lack of random numbers.	5/817 (0.61%)	7/831 (0.84%)	12
5	Major	Medication management	Patients were given wrong medication due to an investigator's negligence.	3/817 (0.37%)	3/831 (0.36%)	6
5	Major	Medication management	Patients were not given medication due to 1) an investigator's negligence; 2) insufficient stock in site.	3/817 (0.37%)	3/831 (0.36%)	6
5	Major	Medication management	Patients were given only 32% of the medication due to an investigator's negligence.	0/817 (0.00%)	1/831 (0.12%)	1

6	Major	Taking contraindicated TCM	One overlapping component of FYTF-919 was used over 14 days or two overlapping components were used over 7 days.	18/817 (2.20%)	16/831 (1.93%)	34
6	Minor	Taking contraindicated TCM	One overlapping component of FYTF-919 was used less than 14 days or two overlapping components were used less than 7 days.	29/817 (3.55%)	43/831 (5.17%)	72
7	Major	Trail endpoint-Primary outcome of D90	Not collected or Patient lost to follow up	15/817 (1.84%)	10/831 (1.20%)	25
10	Minor	Others	The wrong Stratification factor was chosen.	23/817 (2.82%)	23/831 (2.77%)	46
10	Major	Others	Patients took wrong medication due to wrong packaging.	2/817 (0.24%)	1/831 (0.12%)	3
10	Major	Others	Researchers dispensed drugs to patients on their own, rather than following the principle of randomized allocation.	0/817 (0.00%)	1/831 (0.12%)	1

12. Sample size calculations

The sample of 1504 patients are estimated to provide 90% power (α 0.05) to detect a difference in average scores for better outcome between the active and placebo groups of ≥20% (i.e., 0.65 vs. 0.59; SD = 0.32), assuming equal group participations, 6% non-adherence rate, and 10% lost to follow-up. The calculation was based on data from the second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2) where the mean UW-mRS was estimated as 0.59 in control 'less intensive BP control' group. The protocol of CHAIN trial including the sample size estimation has been published on Cerebrovascular Diseases (https://doi.org/10.1159/000534761).

13. Terms of reference of the DSMB

The DSMB was responsible for: safeguarding the interests of trial participants; reviewing the research protocols and plans for data and safety monitoring; reviewing data monitoring reports provided by the study statistician; reviewing the progress of the study and monitoring adherence to the protocol, participant recruitment, outcomes, data quality, complications, and other issues related to participant safety; monitoring the assumptions underlying sample size calculations for the study (Trial Steering Committee [TSC] and Trial Operations Committee [TOC] should be kept blinded) and alert the investigators if they see substantial departures as the data accumulate; ensuring the confidentiality of the study data and the results of monitoring; assessing the safety and efficacy of the interventions during the trial; monitoring the overall conduct of the clinical trial; providing recommendations about stopping or continuing the trial to the trial Steering Committee; contributing to enhancing the integrity of the trial; formulating recommendations in relation to the selection, recruitment, or retention of participants, or their management, or to improving their adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DSMB was advisory to the Steering Committee. The Steering Committee was responsible for promptly reviewing the DSMB recommendations, to decide as to whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct were required.

The DSMB conducted both periodical safety reviews, and a formal interim analysis, by teleconference as follows:

- The first analysis meeting of the DSMB was planned within 6 months from the first patient enrolment of the study to review initial safety data and finalize the format of reports.
- Subsequent safety review meetings were conducted approximately every six months in the initial stages of the trial. Depending on trial progress, the meeting interval was to vary; safety reviews were to concentrate on safety assessment and did include formal testing of the efficacy data.
- One 'Formal Interim Analysis' meeting was planned and undertaken. The purpose was to review data relating to treatment efficacy, patient safety and quality of trial conduct in conjunction with the following scheduled safety review meetings.
- The DSMB will allowed to respond to specific requests made by the CHAIN TSC.

The trial Principal Investigator and other members of the TOC based at The George Institute attended open sessions at the beginning of meetings and were available at the end of meetings

to answer any urgent questions. The date of each DSMB meeting was made available to the unblinded statisticians with at least 6 weeks notice. The unblinded statisticians prepared the DSMB reports and attended the whole meeting to assist with interpretation of the results.

For each DSMB meeting, both safety reviews and the interim analysis; open and closed reports were provided. Open reports, available to all who attended the DSMB meeting, included data on recruitment; study accrual by month and by site, including an assessment of whether recruitment targets are being met; pooled data on eligibility violations; major protocol changes; baseline characteristics (pooled by treatment regimen); completeness of follow-up and compliance; initial brain imaging summary; serious adverse events (including death) summary and detailed list; pooled analysis of primary outcome; details of the number of pending and missing case report forms (including the number of seriously overdue follow-ups), and the number with outstanding data items; any other relevant information (such as updated Cochrane reviews). Closed reports, available only to those attending the closed sessions of the DSMB meeting, included analyses of primary and secondary efficacy endpoints (for interim reviews), subgroup and adjusted analyses, analyses of serious adverse events, and open report analyses that are displayed by intervention group. The reports for the safety reviews were a subset of the reports prepared for the formal interim analysis.

The unblinded statistician(s) from The George Institute for Global Health prepared both the open and closed reports. The open and closed reports provided information that was accurate, with follow-up that was complete to within approximately one month of the date of the DSMB meeting. The Reports were provided to DSMB members 1-2 weeks prior to the date of meetings.

During the period of recruitment into the study, interim analyses of the proportion of patients alive and independent, or dead (at hospital discharge and at 3 months), or with other major outcome events were supplied, in strictest confidence, to all members of the DSMB, along with any other analyses that the DSMB may have requested.

A recommendation to discontinue CHAIN prematurely was to be based upon there being clear evidence that the treatment provides protection or caused harm for an important clinical outcome. The final recommendation to the TSC was at the discretion of the DSMB but based upon agreed standards for the interpretation of interim analysis in clinical trials. The TSC had responsibility for evaluating and implementing the recommendations provided by the DSMB.

A recommendation to modify CHAIN was accompanied by the maximum possible information that the DSMB could provide to the TSC without affecting the integrity of the trial. Once again, the TSC was responsibility for evaluating and implementing any recommendations as they considered appropriate.

The decision to stop the trial temporarily or indefinitely was considered in hand with ensuring safety for the trial participants and the impact premature termination will have on clinical practice. The Haybittle-Peto rule was used as a guide for ‘proof beyond reasonable doubt’ in the monitoring of both efficacy and safety information in the trial.

The DSMB worked on the principle that a difference of at least 3 standard deviations in an interim analysis of a major outcome event (e.g. shift in death and disability according to full range scores on mRS in stroke patients at 90 days) between patients allocated to the active or placebo groups, was a justification for recommending the halting, or modifying, the study before the planned completion of recruitment. This criterion (Peto rule) has the practical

advantage that the exact number of interim analyses is of less importance, and so no fixed schedule was proposed.

Following each DSMB meeting, a recommendation was made to the TSC with the following options in the DSMB statement:

- modification of the study;
- termination of the study early –
  - clear and substantial evidence of benefit
  - data suggests the risk of adverse events substantially outweighs the potential benefits;
- continue the study unchanged;
- additional expert review after which a recommendation will be made;
- additional analyses by the Statistics Group after which a recommendation will be made.

14. Medical review procedures

During the trial, two skilled clinical doctors conducted the medical review. Investigators were required to submit the electronic case report forms (eCRF) within one week after enrolling a patient and within 90 days of follow-up. Medical reviewers then checked the data for completeness, accuracy, and logic. The main verification points included patient eligibility criteria, the consistency of clinical symptoms with NIHSS and GCS scores, intervention and blood pressure levels, the consistency of the mRS score and mRS score at the 90-day follow-up, the consistency of the mRS score and EQ-5D-5L score, and every data point of SAE forms. If any queries were found, the medical reviewers used a secure, password-protected internet-based electronic data capture (EDC) system to send queries and request site investigators to review original data and respond to queries. Before locking the database, all medical review related data must be completed, and all queries must be answered and closed.

15. Per-protocol (PP) analysis set

Patients who have one or more of the following protocol violations will be excluded from the per-protocol (PP) population:

- Age <18 years
- Randomized >48 hours after stroke onset
- NIHSS <2 and GCS 15
- Final diagnosis was not spontaneous ICH
- Patients who were found later in the trial to have received incorrect treatment or incorrect dose of the allocated study drug after confirmation by local investigators.
- Other major protocol violations which have been adjudicated, for example concomitant TCM contains same components of FYTF-919.

16. Assessments of functional outcome and health-related quality of life

The primary outcome was the mean score for disability on the UW-mRS at 90 days. To determine the utility-weighted score, the score on the mRS is weighted according to average values calculated from patient-centered and clinician-centered studies. Based on the algorithm of utility weighing for ICH patients, the following weights are assigned to scores 0 through 6

on the mRS: 0.96, 0.88, 0.74, 0.56, 0.25, -0.11, and 0, respectively. For assessment of health-related quality of life (HRQoL), the EQ-5D-5L questionnaire was used, as assessed directly by a patient or by a proxy-responder. The descriptive system of the EQ-5D defines the state of general health across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three levels (no problems, some/moderate problems, and severe problems). The EQ-5D-5L utility score integrates the ratings of the 5 dimensions into a single score, calculated by using population-based preference weights for each subscale. In the present analysis, we used the weights obtained from the Chinese population. Utility scores express HRQoL quantitatively as a fraction of perfect health, with a score of 1 representing perfect health, a score of 0 representing death. When patients were not able to answer the questionnaire themselves, proxy-responders, such as their caregiver or doctor, were asked to rate the patient's HRQoL. The protocol did not stipulate specifically the process of proxy-responder selection; the decision was opportunistic that arose during a telephone or face-to-face interview between the responsible neurologically competent person (blinded to treatment arm) and the patient or caregiver at the scheduled time of follow-up.

17. Tables

Table S1. Reasons that 7352 patients with acute intracerebral haemorrhage were excluded from participating in the trial*

Reason	N	%
Inclusion criteria		
Refusal	2935	39.9
Diagnosis of intracerebral haemorrhage not confirmed on brain imaging	1447	19.7
Did not meet clinical severity thresholds	935	12.7
Presentation outside the 48 hour time window from last known well	650	8.8
Age <18 years	18	0.2
Exclusion criteria		
Unlikely to potentially benefit from treatment	933	12.7
Other major medical condition	339	4.6
Likely structural cause of the intracerebral haemorrhage	131	1.8
Currently participating in another clinical trial	7	0.1
Women who are know to be pregnant or lactating	6	0.1
Known contraindication to traditional Chinese medicine	4	0.1

*These items are not mutually exclusive. Patients could have been excluded for multiple reasons.

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Table S2. Protocol deviations (PD) / violations (PV) *

Variable	FYTF-919 (N = 815)	Placebo (N = 826)	Overall (N = 1641)
Protocol deviation/violation	141[#] 124/815 (15.2)	164[#] 143/826 (17.3)	305[#] 267/1641 (16.3)
Major protocol violation	83[#] 73/124 (58.9)	85[#] 77/143 (53.8)	168[#] 150/267 (56.2)
Major PV			
Using consent form without regulatory approval	20/83 (24.1)	25/85 (29.4)	45/168 (26.8)
Participants have taken contraindicated Chinese medicine	22/83 (26.5)	21/85 (24.7)	43/168 (25.6)
Inclusion / exclusion criteria not met	13/83 (15.7)	17/85 (20.0)	30/168 (17.9)
Missing data for primary efficacy outcome, including 90-day mRS and EQ-5D-5L (surviving subjects)	15/83 (18.1)	10/85 (11.8)	25/168 (14.9)
Investigator did not follow the protocol for study medication or did not use study medication	5/83 (6.0)	7/85 (8.2)	12/168 (7.1)
The participant was not asked to re-sign the updated consent form after ethics committee approval	5/83 (6.0)	1/85 (1.2)	6/168 (3.6)
All other deviations that may have an impact on the main outcome of the trial, blinding or subject safety shall be analysed on a case-by-case basis	2/83 (2.4)	2/85 (2.4)	4/168 (2.4)
Using consent form without ethics committee approval	1/83 (1.2)	2/85 (2.4)	3/168 (1.8)
Minor protocol deviation	58[#] 57/124 (46.0)	79[#] 76/143 (53.1)	137[#] 133/267 (49.8)
Minor PD			
Participants have taken Contraindicative Chinese medicine	29/58 (50.0)	45/79 (57.0)	74/137 (54.0)
Other	23/58 (39.7)	27/79 (34.2)	50/137 (36.5)
Study medication	6/58 (10.3)	7/79 (8.9)	13/137 (9.5)

Data are not mutually exclusive and presented as n (%). EQ-5D-5L=EuroQol health-related quality of life questionnaire, mRS=modified Rankin scale.

*There were 95 patients excluded from the per protocol dataset for reasons of major PV: (i) taken a contraindicated Chinese medicine; (ii) inclusion/exclusion criteria not met, and/or (iii) the investigator did not follow the protocol in the use of the study medication. Participants were also excluded from per protocol dataset if they did not take any study medication at all (0 bottles used).

Table S3. Additional clinical features, medical history and use of medications in patients with acute intracerebral haemorrhage*

Variable	FYTF-919 (N=815)	Placebo (N=826)
Mean total TCM assessment score (1-5)	1.1 (1.3)	1.1 (1.3)
Individual components of TMC score		
Anxiety	96/780 (12.3)	92/788 (11.7)
Red face / temperature >37.5°	156/780 (20.0)	162/787 (20.6)
Dry mouth / bad breath	188/755 (24.3)	197/783 (25.2)
Yellow tongue coating	169/760 (22.2)	179/773 (23.2)
Red tongue coating	264/760 (34.7)	265/772 (34.3)
No stool in last 48 hours	237/781 (30.3)	269/785 (34.3)
Height, cm	166 (8)	166 (8)
Weight, kg	66 (13)	68 (12)
MBI, kg/m^2	24 (4)	24 (3)
Heart rate	80 (15)	81 (15)
Respiratory rate	19 (4)	19 (4)
Medical history- n (%)		
Atrial fibrillation	1 (0.1)	6 (0.7)
History of hyperlipidaemia	10/815 (1.2)	9/826 (1.1)
Current smoker	69 (17)	73 (18)
Antihypertension drugs used in those with hypertension	508/539 (94.2)	540/572 (94.4)
Type of antihypertension -		
ACE-I or ARB	37/508 (7.3)	51/540 (9.4)
Diuretic	2/508 (0.4)	5/540 (0.9)
Calcium channel blocker	85/508 (16.7)	98/540 (18.1)
Beta-blocker	12/508 (2.4)	13/540 (2.4)
Reserpine Co	5/386 (1.3)	4/395 (1.0)
Other	386/508 (76.0)	395/540 (73.1)
Unknown	381/386 (98.7)	391/395 (99.0)
Type of antiplatelet agent		
Aspirin	31/35 (88.6)	25/29 (86.2)
Clopidogrel	8/35 (22.6)	6/299 (20.7)
Cilostazol	1/35 (2.9)	3/29 (10.3)
Blood glucose lowering agents used	24/69 (34.8)	35/73 (47.9)
Insulin	1/24 (4.2)	0/35 (0)

Data are n (%)

*ACE-I indicates angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker, TMC traditional Chinese medicine

Table S4. Additional information on the characteristics of intracerebral haemorrhage on computerised tomographic (CT) brain imaging

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N = 1641)
Hour from onset to CT scan			
n	769	780	1549
Mean (SD)	5.9 (7.5)	5.7 (6.8)	5.8 (7.1)
Median (Q1; Q3)	3.2 (1.8; 6.1)	3.2 (1.8; 6.1)	3.2 (1.8; 6.1)
min max	0 55	0 44	0 55
Haematoma volume, ml			
n	775	792	1567
Mean (SD)	24.6 (22.8)	23.2 (21.9)	23.9 (22.3)
Median (Q1; Q3)	18.0 (8.0; 35.0)	16.9 (8.1; 30.0)	17.6 (8.0; 32.0)
min max	0 182	0 181	0 182
Haematoma location			
Left	428/810 (52.8)	399/821 (48.6)	827/1631 (50.7)
Right	358/810 (44.2)	400/821 (48.7)	758/1631 (46.5)
Median	24/810 (3.0)	22/821 (2.7)	46/1631 (2.8)

Data are n (%), mean (SD) or median (IQR)

Table S5. Characteristics of participants aged <65 years

Characteristics	FYTF-919 (N = 451)	Placebo (N = 494)	Overall (N = 945)
Age (Years)			
n	451	494	945
Mean (SD)	53.5 (7.62)	53.4 (7.78)	53.4 (7.70)
Median (Q1; Q3)	55.0 (49.0; 59.0)	55.0 (49.0; 59.0)	55.0 (49.0; 59.0)
min max	29 64	18 64	18 64
Sex			
Male	307/451 (68.1%)	355/494 (71.9%)	662/945 (70.1%)
Female	144/451 (31.9%)	139/494 (28.1%)	283/945 (29.9%)
Ethnicity			
Han	436/451 (96.7%)	479/494 (97.0%)	915/945 (96.8%)
Non-Han Minorities	15/451 (3.3%)	15/494 (3.0%)	30/945 (3.2%)
Height (cm)			
n	373	416	789
Mean (SD)	166.6 (7.52)	168.1 (7.25)	167.4 (7.41)
Median (Q1; Q3)	169.0 (160.0; 172.0)	170.0 (163.0; 174.0)	170.0 (160.0; 173.0)
min max	145 183	140 183	140 183
Weight (Kg)			
n	321	368	689
Mean (SD)	69.8 (12.50)	70.7 (11.36)	70.3 (11.91)
Median (Q1; Q3)	70.0 (60.0; 80.0)	70.0 (62.5; 79.5)	70.0 (60.5; 80.0)
min max	40 120	40 115	40 120

Characteristics	FYTF-919 (N = 451)	Placebo (N = 494)	Overall (N = 945)
BMI (Kg/m2)			
n	320	367	687
Mean (SD)	24.9 (3.73)	24.9 (3.22)	24.9 (3.46)
Median (Q1; Q3)	24.8 (22.5; 26.8)	24.6 (22.8; 26.8)	24.7 (22.6; 26.8)
min max	17 46	17 36	17 46
Current smoking			
No	318/451 (70.5%)	347/493 (70.4%)	665/944 (70.4%)
Yes	133/451 (29.5%)	146/493 (29.6%)	279/944 (29.6%)
Current drinking			
No	313/451 (69.4%)	343/493 (69.6%)	656/944 (69.5%)
Yes	138/451 (30.6%)	150/493 (30.4%)	288/944 (30.5%)
SBP on arrival			
n	449	492	941
Mean (SD)	170.7 (28.79)	171.9 (28.99)	171.4 (28.88)
Median (Q1; Q3)	170.0 (150.0; 190.0)	173.0 (149.0; 191.0)	171.0 (150.0; 191.0)
min max	107 265	102 245	102 265
DBP on arrival			
n	449	492	941
Mean (SD)	100.6 (18.77)	102.5 (20.70)	101.6 (19.81)
Median (Q1; Q3)	100.0 (89.0; 111.0)	101.0 (88.0; 115.0)	100.0 (89.0; 113.0)
min max	44 167	11 197	11 197

Characteristics	FYTF-919 (N = 451)	Placebo (N = 494)	Overall (N = 945)
Heart rate on arrival			
n	450	493	943
Mean (SD)	80.4 (15.32)	82.0 (15.84)	81.3 (15.60)
Median (Q1; Q3)	80.0 (70.0; 88.0)	80.0 (72.0; 90.0)	80.0 (70.0; 90.0)
min max	47 208	20 150	20 208
Respiratory rate on arrival			
n	441	481	922
Mean (SD)	18.9 (2.66)	19.1 (3.51)	19.0 (3.13)
Median (Q1; Q3)	19.0 (18.0; 20.0)	19.0 (18.0; 20.0)	19.0 (18.0; 20.0)
min max	10 35	10 76	10 76
Body temperature on arrival			
n	451	492	943
Mean (SD)	36.58 (0.371)	36.61 (0.368)	36.60 (0.370)
Median (Q1; Q3)	36.50 (36.30; 36.80)	36.60 (36.50; 36.80)	36.60 (36.50; 36.80)
min max	35.7 39.8	35.0 39.2	35.0 39.8
first GCS on arrival			
n	429	475	904
Mean (SD)	11.6 (2.84)	11.6 (2.95)	11.6 (2.90)
Median (Q1; Q3)	12.0 (10.0; 14.0)	12.0 (10.0; 14.0)	12.0 (10.0; 14.0)
min max	3 15	3 15	3 15
first NIHSS on arrival			

Characteristics	FYTF-919 (N = 451)	Placebo (N = 494)	Overall (N = 945)
n	447	488	935
Mean (SD)	16.6 (8.43)	16.1 (8.00)	16.3 (8.20)
Median (Q1; Q3)	15.0 (11.0; 21.0)	15.0 (10.0; 20.0)	15.0 (10.0; 21.0)
min max	0 41	1 42	0 42
NIHSS category			
NIHSS >=15	243/447 (54.4%)	265/488 (54.3%)	508/935 (54.3%)
NIHSS < 15	204/447 (45.6%)	223/488 (45.7%)	427/935 (45.7%)
First IMP method			
Oral admission（awake，33ml/time，tid）	205/441 (46.5%)	241/491 (49.1%)	446/932 (47.9%)
Nasogastric tube（coma，25ml/time，q6h）	236/441 (53.5%)	250/491 (50.9%)	486/932 (52.1%)
Previous Hypertension	301/451 (66.7%)	335/491 (68.2%)	636/942 (67.5%)
Antihypertensive medication	278/301 (92.4%)	314/335 (93.7%)	592/636 (93.1%)
ACEI ARB	17/278 (6.1%)	29/314 (9.2%)	46/592 (7.8%)
Beta blocker	7/278 (2.5%)	9/314 (2.9%)	16/592 (2.7%)
Ca antagonist	31/278 (11.2%)	63/314 (20.1%)	94/592 (15.9%)
Diuretics	1/278 (0.4%)	2/314 (0.6%)	3/592 (0.5%)

Characteristics	FYTF-919 (N = 451)	Placebo (N = 494)	Overall (N = 945)
Other antihypertensives	227/278 (81.7%)	225/314 (71.7%)	452/592 (76.4%)
Reserpine Co	1/227 (0.4%)	0/225 (0.0%)	1/452 (0.2%)
Unknown	226/227 (99.6%)	225/225 (100.0%)	451/452 (99.8%)
Previous Diabetes	32/451 (7.1%)	46/494 (9.3%)	78/945 (8.3%)
Antidiabetic medication	10/32 (31.3%)	25/46 (54.3%)	35/78 (44.9%)
Insulin	0/10 (0.0%)	0/25 (0.0%)	0/35 (0.0%)
Biguanide	1/10 (10.0%)	1/25 (4.0%)	2/35 (5.7%)
Sulfonylurea	0/10 (0.0%)	0/25 (0.0%)	0/35 (0.0%)
Glycosidase inhibitor	1/10 (10.0%)	0/25 (0.0%)	1/35 (2.9%)
Other	8/10 (80.0%)	24/25 (96.0%)	32/35 (91.4%)
Euphridine	1/8 (12.5%)	0/24 (0.0%)	1/32 (3.1%)
Liraglutide	0/8 (0.0%)	1/24 (4.2%)	1/32 (3.1%)
Repaglinide	1/8 (12.5%)	0/24 (0.0%)	1/32 (3.1%)
Unknown	6/8 (75.0%)	23/24 (95.8%)	29/32 (90.6%)
Previous Hyperlipidemia	4/451 (0.9%)	5/494 (1.0%)	9/945 (1.0%)

Characteristics	FYTF-919 (N = 451)	Placebo (N = 494)	Overall (N = 945)
Lipid lowering agent	3/4 (75.0%)	3/5 (60.0%)	6/9 (66.7%)
Statin	3/3 (100.0%)	0/3 (0.0%)	3/6 (50.0%)
Cholesterol absorption inhibitor	0/3 (0.0%)	0/3 (0.0%)	0/6 (0.0%)
PCSK9 inhibitor	0/3 (0.0%)	0/3 (0.0%)	0/6 (0.0%)
Other (All unknown)	0/3 (0.0%)	3/3 (100.0%)	3/6 (50.0%)
Previous Coronary Heart Disease	13/451 (2.9%)	11/494 (2.2%)	24/945 (2.5%)
Previous Atrial Fibrillation	0/451 (0.0%)	1/494 (0.2%)	1/945 (0.1%)
Any anticoagulant treatment	1/451 (0.2%)	1/494 (0.2%)	2/945 (0.2%)
Any antiplatelet treatment	14/451 (3.1%)	13/494 (2.6%)	27/945 (2.9%)
Aspirin	14/14 (100.0%)	12/13 (92.3%)	26/27 (96.3%)
Clopidogrel	1/14 (7.1%)	4/13 (30.8%)	5/27 (18.5%)
Other	0/14 (0.0%)	1/13 (7.7%)	1/27 (3.7%)
Total TCM score (TCM 1-5)			
n	426	466	892

Characteristics	FYTF-919 (N = 451)	Placebo (N = 494)	Overall (N = 945)
Mean (SD)	1.1 (1.28)	1.1 (1.26)	1.1 (1.27)
Median (Q1; Q3)	1.0 (0.0; 2.0)	1.0 (0.0; 2.0)	1.0 (0.0; 2.0)
min max	0 5	0 5	0 5
Anxiety	62/425 (14.6%)	57/466 (12.2%)	119/891 (13.4%)
Red face/T>37.5	87/425 (20.5%)	98/465 (21.1%)	185/890 (20.8%)
Dry mouth/Bad breath	108/420 (25.7%)	116/463 (25.1%)	224/883 (25.4%)
Yellow tongue coating	97/410 (23.7%)	108/456 (23.7%)	205/866 (23.7%)
Red tongue coating	132/410 (32.2%)	151/456 (33.1%)	283/866 (32.7%)
No Stool in the last 48h	131/427 (30.7%)	175/466 (37.6%)	306/893 (34.3%)

Table S6. Characteristics of participants aged ≥65 years

Characteristics	FYTF-919 (N = 364)	Placebo (N = 332)	Overall (N = 696)
Age (Years)			
n	364	332	696
Mean (SD)	72.9 (6.27)	73.0 (5.88)	73.0 (6.09)
Median (Q1; Q3)	72.0 (68.0; 76.5)	72.0 (68.0; 77.0)	72.0 (68.0; 77.0)
min max	65 97	65 94	65 97
Sex			
Male	221/364 (60.7%)	196/332 (59.0%)	417/696 (59.9%)
Female	143/364 (39.3%)	136/332 (41.0%)	279/696 (40.1%)
Ethnicity			
Han	354/364 (97.3%)	318/332 (95.8%)	672/696 (96.6%)
Non-Han Minorities	10/364 (2.7%)	14/332 (4.2%)	24/696 (3.4%)
Height (cm)			
n	321	299	620
Mean (SD)	164.5 (8.24)	164.0 (8.10)	164.2 (8.17)
Median (Q1; Q3)	165.0 (158.0; 170.0)	165.0 (158.0; 170.0)	165.0 (158.0; 170.0)
min max	140 182	145 180	140 182
Weight (Kg)			
n	296	273	569
Mean (SD)	62.7 (11.62)	63.1 (11.44)	62.9 (11.53)
Median (Q1; Q3)	61.2 (55.0; 70.0)	62.0 (55.0; 70.0)	62.0 (55.0; 70.0)

Characteristics	FYTF-919 (N = 364)	Placebo (N = 332)	Overall (N = 696)
min max	33 90	30 95	30 95
BMI (Kg/m2)			
n	295	273	568
Mean (SD)	23.0 (3.24)	23.4 (3.41)	23.2 (3.33)
Median (Q1; Q3)	23.0 (20.8; 25.2)	23.4 (21.0; 25.5)	23.1 (20.8; 25.4)
min max	15 33	13 35	13 35
Current smoking			
No	286/364 (78.6%)	253/332 (76.2%)	539/696 (77.4%)
Yes	78/364 (21.4%)	79/332 (23.8%)	157/696 (22.6%)
Current drinking			
No	295/363 (81.3%)	266/332 (80.1%)	561/695 (80.7%)
Yes	68/363 (18.7%)	66/332 (19.9%)	134/695 (19.3%)
SBP on arrival			
n	363	332	695
Mean (SD)	172.8 (30.07)	171.7 (28.97)	172.2 (29.53)
Median (Q1; Q3)	171.0 (153.0; 191.0)	170.0 (150.0; 192.0)	170.0 (151.0; 192.0)
min max	82 257	91 261	82 261
DBP on arrival			
n	363	332	695
Mean (SD)	95.5 (18.81)	93.1 (16.59)	94.4 (17.81)
Median (Q1; Q3)	95.0 (82.0; 107.0)	92.0 (80.0; 104.0)	94.0 (81.0; 105.0)

Characteristics	FYTF-919 (N = 364)	Placebo (N = 332)	Overall (N = 696)
min max	42 160	54 179	42 179
Heart rate on arrival			
n	363	332	695
Mean (SD)	78.4 (14.53)	78.4 (14.29)	78.4 (14.41)
Median (Q1; Q3)	79.0 (68.0; 87.0)	79.0 (68.0; 86.0)	79.0 (68.0; 87.0)
min max	46 134	20 140	20 140
Respiratory rate on arrival			
n	358	324	682
Mean (SD)	19.6 (4.78)	19.7 (3.69)	19.6 (4.30)
Median (Q1; Q3)	20.0 (18.0; 20.0)	20.0 (18.0; 20.0)	20.0 (18.0; 20.0)
min max	12 98	12 71	12 98
Body temperature on arrival			
n	364	332	696
Mean (SD)	36.60 (0.374)	36.62 (0.444)	36.61 (0.408)
Median (Q1; Q3)	36.50 (36.40; 36.80)	36.50 (36.40; 36.80)	36.50 (36.40; 36.80)
min max	35.7 39.1	35.5 39.8	35.5 39.8
first GCS on arrival			
n	355	316	671
Mean (SD)	11.6 (2.76)	11.6 (2.95)	11.6 (2.85)
Median (Q1; Q3)	12.0 (10.0; 14.0)	12.0 (9.5; 14.0)	12.0 (10.0; 14.0)
min max	3 15	3 15	3 15

Characteristics	FYTF-919 (N = 364)	Placebo (N = 332)	Overall (N = 696)
first NIHSS on arrival			
n	364	330	694
Mean (SD)	15.9 (7.53)	16.5 (8.26)	16.2 (7.89)
Median (Q1; Q3)	15.5 (10.0; 20.0)	15.0 (10.0; 21.0)	15.0 (10.0; 20.0)
min max	0 42	1 40	0 42
NIHSS category			
NIHSS >=15	198/364 (54.4%)	177/330 (53.6%)	375/694 (54.0%)
NIHSS < 15	166/364 (45.6%)	153/330 (46.4%)	319/694 (46.0%)
First IMP method			
Oral admission（awake，33ml/time，tid）	195/362 (53.9%)	162/330 (49.1%)	357/692 (51.6%)
Nasogastric tube（coma，25ml/time，q6h）	167/362 (46.1%)	168/330 (50.9%)	335/692 (48.4%)
Previous Hypertension	238/362 (65.7%)	237/332 (71.4%)	475/694 (68.4%)
Antihypertensive medication	230/238 (96.6%)	226/237 (95.4%)	456/475 (96.0%)
ACEI ARB	20/230 (8.7%)	22/226 (9.7%)	42/456 (9.2%)
Beta blocker	5/230 (2.2%)	4/226 (1.8%)	9/456 (2.0%)
Ca antagonist	54/230 (23.5%)	35/226 (15.5%)	89/456 (19.5%)
Diuretics	1/230 (0.4%)	3/226 (1.3%)	4/456 (0.9%)

Characteristics	FYTF-919 (N = 364)	Placebo (N = 332)	Overall (N = 696)
Other antihypertensives	159/230 (69.1%)	170/226 (75.2%)	329/456 (72.1%)
Reserpine Co	4/159 (2.5%)	4/170 (2.4%)	8/329 (2.4%)
Unknown	155/159 (97.5%)	166/170 (97.6%)	321/329 (97.6%)
Previous Diabetes	37/364 (10.2%)	27/331 (8.2%)	64/695 (9.2%)
Antidiabetic medication	14/37 (37.8%)	10/27 (37.0%)	24/64 (37.5%)
Insulin	1/14 (7.1%)	0/10 (0.0%)	1/24 (4.2%)
Biguanide	2/14 (14.3%)	1/10 (10.0%)	3/24 (12.5%)
Sulfonylurea	1/14 (7.1%)	0/10 (0.0%)	1/24 (4.2%)
Glycosidase inhibitor	1/14 (7.1%)	0/10 (0.0%)	1/24 (4.2%)
Other	12/14 (85.7%)	9/10 (90.0%)	21/24 (87.5%)
Unknown	12/12 (100.0%)	9/9 (100.0%)	21/21 (100.0%)
Previous Hyperlipidemia	6/364 (1.6%)	4/332 (1.2%)	10/696 (1.4%)
Lipid lowering agent	5/6 (83.3%)	4/4 (100.0%)	9/10 (90.0%)

Characteristics	FYTF-919 (N = 364)	Placebo (N = 332)	Overall (N = 696)
Statin	2/5 (40.0%)	3/4 (75.0%)	5/9 (55.6%)
Cholesterol absorption inhibitor	0/5 (0.0%)	0/4 (0.0%)	0/9 (0.0%)
PCSK9 inhibitor	0/5 (0.0%)	0/4 (0.0%)	0/9 (0.0%)
Other (All unknown)	3/5 (60.0%)	1/4 (25.0%)	4/9 (44.4%)
Previous Coronary Heart Disease	30/364 (8.2%)	19/332 (5.7%)	49/696 (7.0%)
Previous Atrial Fibrillation	1/364 (0.3%)	5/332 (1.5%)	6/696 (0.9%)
Any anticoagular treatment	0/364 (0.0%)	2/332 (0.6%)	2/696 (0.3%)
Any antiplatelet treatment	21/364 (5.8%)	16/332 (4.8%)	37/696 (5.3%)
Aspirin	17/21 (81.0%)	13/16 (81.3%)	30/37 (81.1%)
Clopidogrel	7/21 (33.3%)	2/16 (12.5%)	9/37 (24.3%)
Other	1/21 (4.8%)	2/16 (12.5%)	3/37 (8.1%)
Total TCM score (TCM 1-5)			
n	355	322	677
Mean (SD)	1.1 (1.21)	1.1 (1.27)	1.1 (1.24)
Median (Q1; Q3)	1.0 (0.0; 2.0)	1.0 (0.0; 2.0)	1.0 (0.0; 2.0)

Characteristics	FYTF-919 (N = 364)	Placebo (N = 332)	Overall (N = 696)
min max	0 5	0 5	0 5
Anxiety	34/355 (9.6%)	35/322 (10.9%)	69/677 (10.2%)
Red face/T>37.5	69/355 (19.4%)	64/322 (19.9%)	133/677 (19.6%)
Dry mouth/Bad breath	80/355 (22.5%)	81/320 (25.3%)	161/675 (23.9%)
Yellow tongue coating	72/350 (20.6%)	71/317 (22.4%)	143/667 (21.4%)
Red tongue coating	132/350 (37.7%)	114/316 (36.1%)	246/666 (36.9%)
No Stool in the last 48h	106/354 (29.9%)	94/319 (29.5%)	200/673 (29.7%)

Table S7. Characteristics of female participants

Characteristics	FYTF-919 (N = 287)	Placebo (N = 275)	Overall (N = 562)
Age (Years)			
n	287	275	562
Mean (SD)	64.0 (11.35)	64.5 (11.04)	64.3 (11.19)
Median (Q1; Q3)	64.0 (56.0; 73.0)	64.0 (56.0; 72.0)	64.0 (56.0; 72.0)
min max	29 97	36 94	29 97
Ethnicity			
Han	284/287 (99.0%)	270/275 (98.2%)	554/562 (98.6%)
Non-Han Minorities	3/287 (1.0%)	5/275 (1.8%)	8/562 (1.4%)
Height (cm)			
n	241	223	464
Mean (SD)	157.9 (4.95)	158.0 (5.24)	158.0 (5.09)
Median (Q1; Q3)	158.0 (155.0; 160.0)	158.0 (155.0; 162.0)	158.0 (155.0; 160.0)
min max	140 175	145 171	140 175
Weight (Kg)			
n	210	198	408
Mean (SD)	58.4 (10.69)	60.5 (10.05)	59.4 (10.43)
Median (Q1; Q3)	57.5 (50.0; 65.0)	60.0 (55.0; 65.0)	60.0 (52.0; 65.0)
min max	33 110	30 95	30 110
BMI (Kg/m2)			
n	209	198	407
Mean (SD)	23.4 (3.99)	24.1 (3.55)	23.8 (3.80)

Characteristics	FYTF-919 (N = 287)	Placebo (N = 275)	Overall (N = 562)
Median (Q1; Q3)	22.9 (20.5; 25.4)	23.9 (22.0; 26.2)	23.5 (21.2; 25.9)
min max	15 46	13 35	13 46
Current smoking			
No	278/287 (96.9%)	265/275 (96.4%)	543/562 (96.6%)
Yes	9/287 (3.1%)	10/275 (3.6%)	19/562 (3.4%)
Current drinking			
No	282/286 (98.6%)	267/275 (97.1%)	549/561 (97.9%)
Yes	4/286 (1.4%)	8/275 (2.9%)	12/561 (2.1%)
SBP on arrival			
n	287	275	562
Mean (SD)	171.1 (29.06)	171.1 (29.69)	171.1 (29.34)
Median (Q1; Q3)	171.0 (150.0; 191.0)	171.0 (150.0; 189.0)	171.0 (150.0; 190.0)
min max	82 265	91 261	82 265
DBP on arrival			
n	287	275	562
Mean (SD)	95.0 (17.53)	95.4 (18.69)	95.2 (18.09)
Median (Q1; Q3)	95.0 (84.0; 105.0)	95.0 (82.0; 106.0)	95.0 (83.0; 105.0)
min max	42 153	60 197	42 197
Heart rate on arrival			
n	287	275	562
Mean (SD)	79.3 (15.40)	81.2 (14.84)	80.2 (15.14)

Characteristics	FYTF-919 (N = 287)	Placebo (N = 275)	Overall (N = 562)
Median (Q1; Q3)	80.0 (69.0; 86.0)	80.0 (72.0; 89.0)	80.0 (70.0; 88.0)
min max	48 208	20 150	20 208
Respiratory rate on arrival			
n	279	271	550
Mean (SD)	18.9 (2.34)	19.6 (5.31)	19.3 (4.09)
Median (Q1; Q3)	19.0 (18.0; 20.0)	19.0 (18.0; 20.0)	19.0 (18.0; 20.0)
min max	12 28	11 76	11 76
Body temperature on arrival			
n	287	275	562
Mean (SD)	36.56 (0.402)	36.64 (0.462)	36.60 (0.433)
Median (Q1; Q3)	36.50 (36.30; 36.80)	36.60 (36.50; 36.80)	36.50 (36.40; 36.80)
min max	35.7 39.8	35.8 39.8	35.7 39.8
first GCS on arrival			
n	276	258	534
Mean (SD)	11.3 (3.04)	11.4 (3.04)	11.4 (3.04)
Median (Q1; Q3)	12.0 (9.0; 14.0)	12.0 (9.0; 14.0)	12.0 (9.0; 14.0)
min max	3 15	3 15	3 15
first NIHSS on arrival			
n	284	272	556
Mean (SD)	16.5 (8.29)	16.8 (8.68)	16.6 (8.48)
Median (Q1; Q3)	15.0 (10.0; 21.0)	15.0 (10.0; 21.0)	15.0 (10.0; 21.0)
min max	1 41	1 38	1 41

Characteristics	FYTF-919 (N = 287)	Placebo (N = 275)	Overall (N = 562)
NIHSS category			
NIHSS >=15	149/284 (52.5%)	147/272 (54.0%)	296/556 (53.2%)
NIHSS < 15	135/284 (47.5%)	125/272 (46.0%)	260/556 (46.8%)
Time from onset to arrival (hour)			
n	287	275	562
Mean (SD)	5.5 (7.00)	5.1 (5.98)	5.3 (6.52)
Median (Q1; Q3)	3.0 (1.9; 6.0)	3.1 (1.7; 5.6)	3.0 (1.9; 5.9)
min max	0 45	0 37	0 45
Time from onset to randomization (hour)			
n	287	275	562
Mean (SD)	18.3 (12.98)	17.4 (11.74)	17.9 (12.39)
Median (Q1; Q3)	15.3 (7.0; 26.8)	15.5 (7.1; 25.5)	15.4 (7.0; 26.2)
min max	2 56	1 57	1 57
Time from onset to first medicine given (hour)			
n	285	272	557
Mean (SD)	22.7 (14.35)	22.1 (13.45)	22.4 (13.91)
Median (Q1; Q3)	20.0 (11.0; 31.6)	20.2 (10.6; 29.8)	20.0 (10.9; 31.0)
min max	3 89	2 75	2 89
First IMP method			
Oral admission（awake，33ml/time，tid）	139/285 (48.8%)	124/273 (45.4%)	263/558 (47.1%)

Characteristics	FYTF-919 (N = 287)	Placebo (N = 275)	Overall (N = 562)
Nasogastric tube（coma，25ml/time, q6h）	146/285 (51.2%)	149/273 (54.6%)	295/558 (52.9%)
Previous Hypertension	197/287 (68.6%)	209/273 (76.6%)	406/560 (72.5%)
Antihypertensive medication	187/197 (94.9%)	197/209 (94.3%)	384/406 (94.6%)
ACEI ARB	16/187 (8.6%)	24/197 (12.2%)	40/384 (10.4%)
Beta blocker	4/187 (2.1%)	4/197 (2.0%)	8/384 (2.1%)
Ca antagonist	34/187 (18.2%)	35/197 (17.8%)	69/384 (18.0%)
Diuretics	1/187 (0.5%)	2/197 (1.0%)	3/384 (0.8%)
Other antihypertensives	140/187 (74.9%)	141/197 (71.6%)	281/384 (73.2%)
Reserpine Co	3/140 (2.1%)	2/141 (1.4%)	5/281 (1.8%)
Unknown	137/140 (97.9%)	139/141 (98.6%)	276/281 (98.2%)
Previous Diabetes	26/287 (9.1%)	29/275 (10.5%)	55/562 (9.8%)
Antidiabetic medication	10/26 (38.5%)	14/29 (48.3%)	24/55 (43.6%)
Insulin	0/10 (0.0%)	0/14 (0.0%)	0/24 (0.0%)

Characteristics	FYTF-919 (N = 287)	Placebo (N = 275)	Overall (N = 562)
Biguanide	1/10 (10.0%)	1/14 (7.1%)	2/24 (8.3%)
Sulfonylurea	1/10 (10.0%)	0/14 (0.0%)	1/24 (4.2%)
Glycosidase inhibitor	1/10 (10.0%)	0/14 (0.0%)	1/24 (4.2%)
Other	8/10 (80.0%)	13/14 (92.9%)	21/24 (87.5%)
Liraglutide	0/8 (0.0%)	1/13 (7.7%)	1/21 (4.8%)
Repaglinide	1/8 (12.5%)	0/13 (0.0%)	1/21 (4.8%)
Unknown	7/8 (87.5%)	12/13 (92.3%)	19/21 (90.5%)
Previous Hyperlipidemia	0/287 (0.0%)	3/275 (1.1%)	3/562 (0.5%)
Lipid lowering agent	0/0 (0.0%)	3/3 (100.0%)	3/3 (100.0%)
Statin	0/0 (0.0%)	2/3 (66.7%)	2/3 (66.7%)
Cholesterol absorption inhibitor	0/0 (0.0%)	0/3 (0.0%)	0/3 (0.0%)
PCSK9 inhibitor	0/0 (0.0%)	0/3 (0.0%)	0/3 (0.0%)
Other (All unknown)	0/0 (0.0%)	1/3 (33.3%)	1/3 (33.3%)
Previous Coronary Heart Disease	20/287 (7.0%)	20/275 (7.3%)	40/562 (7.1%)

Characteristics	FYTF-919 (N = 287)	Placebo (N = 275)	Overall (N = 562)
Previous Atrial Fibrillation	0/287 (0.0%)	3/275 (1.1%)	3/562 (0.5%)
Any anticoagular treatment	0/287 (0.0%)	2/275 (0.7%)	2/562 (0.4%)
Any antiplatelet treatment	12/287 (4.2%)	11/275 (4.0%)	23/562 (4.1%)
Aspirin	11/12 (91.7%)	9/11 (81.8%)	20/23 (87.0%)
Clopidogrel	3/12 (25.0%)	1/11 (9.1%)	4/23 (17.4%)
Other	0/12 (0.0%)	2/11 (18.2%)	2/23 (8.7%)
Total TCM score (TCM 1-5)			
n	273	260	533
Mean (SD)	0.9 (1.15)	1.0 (1.21)	1.0 (1.18)
Median (Q1; Q3)	0.0 (0.0; 2.0)	1.0 (0.0; 2.0)	1.0 (0.0; 2.0)
min max	0 5	0 5	0 5
Anxiety	23/273 (8.4%)	26/260 (10.0%)	49/533 (9.2%)
Red face/T>37.5	46/273 (16.8%)	51/260 (19.6%)	97/533 (18.2%)
Dry mouth/Bad breath	64/273 (23.4%)	59/259 (22.8%)	123/532 (23.1%)
Yellow tongue coating	40/265 (15.1%)	46/256 (18.0%)	86/521 (16.5%)

Characteristics	FYTF-919 (N = 287)	Placebo (N = 275)	Overall (N = 562)
Red tongue coating	82/265 (30.9%)	81/256 (31.6%)	163/521 (31.3%)
No Stool in the last 48h	76/272 (27.9%)	88/258 (34.1%)	164/530 (30.9%)

Table S8. Characteristics of male participants

Characteristics	FYTF-919 (N = 528)	Placebo (N = 551)	Overall (N = 1079)
Age (Years)			
n	528	551	1079
Mean (SD)	61.2 (12.19)	59.6 (12.06)	60.4 (12.14)
Median (Q1; Q3)	61.0 (53.5; 70.0)	59.0 (52.0; 68.0)	60.0 (53.0; 69.0)
min max	29 97	18 90	18 97
Ethnicity			
Han	506/528 (95.8%)	527/551 (95.6%)	1033/1079 (95.7%)
Non-Han Minorities	22/528 (4.2%)	24/551 (4.4%)	46/1079 (4.3%)
Height (cm)			
n	453	492	945
Mean (SD)	169.8 (5.85)	170.1 (5.66)	170.0 (5.75)
Median (Q1; Q3)	170.0 (167.0; 175.0)	170.0 (167.0; 175.0)	170.0 (167.0; 175.0)
min max	145 183	140 183	140 183
Weight (Kg)			
n	407	443	850
Mean (SD)	70.6 (11.45)	70.6 (11.46)	70.6 (11.45)
Median (Q1; Q3)	70.0 (62.0; 80.0)	70.0 (62.5; 80.0)	70.0 (62.0; 80.0)
min max	40 120	35 115	35 120
BMI (Kg/m2)			
n	406	442	848
Mean (SD)	24.3 (3.39)	24.4 (3.31)	24.3 (3.34)

Characteristics	FYTF-919 (N = 528)	Placebo (N = 551)	Overall (N = 1079)
Median (Q1; Q3)	24.2 (22.1; 26.1)	24.2 (22.1; 26.4)	24.2 (22.1; 26.2)
min max	17 42	13 36	13 42
Current smoking			
No	326/528 (61.7%)	335/550 (60.9%)	661/1078 (61.3%)
Yes	202/528 (38.3%)	215/550 (39.1%)	417/1078 (38.7%)
Current drinking			
No	326/528 (61.7%)	342/550 (62.2%)	668/1078 (62.0%)
Yes	202/528 (38.3%)	208/550 (37.8%)	410/1078 (38.0%)
SBP on arrival			
n	525	549	1074
Mean (SD)	172.0 (29.55)	172.2 (28.61)	172.1 (29.06)
Median (Q1; Q3)	170.0 (150.0; 190.0)	171.0 (150.0; 192.0)	170.5 (150.0; 192.0)
min max	106 257	102 246	102 257
DBP on arrival			
n	525	549	1074
Mean (SD)	100.2 (19.44)	100.3 (19.98)	100.3 (19.71)
Median (Q1; Q3)	99.0 (88.0; 112.0)	99.0 (86.0; 112.0)	99.0 (87.0; 112.0)
min max	44 167	11 179	11 179
Heart rate on arrival			
n	526	550	1076
Mean (SD)	79.6 (14.78)	80.3 (15.57)	80.0 (15.19)

Characteristics	FYTF-919 (N = 528)	Placebo (N = 551)	Overall (N = 1079)
Median (Q1; Q3)	80.0 (69.0; 88.0)	79.0 (70.0; 89.0)	80.0 (70.0; 88.0)
min max	46 134	40 149	40 149
Respiratory rate on arrival			
n	520	534	1054
Mean (SD)	19.3 (4.35)	19.2 (2.26)	19.3 (3.45)
Median (Q1; Q3)	19.0 (18.0; 20.0)	19.0 (18.0; 20.0)	19.0 (18.0; 20.0)
min max	10 98	10 30	10 98
Body temperature on arrival			
n	528	549	1077
Mean (SD)	36.61 (0.355)	36.61 (0.365)	36.61 (0.360)
Median (Q1; Q3)	36.60 (36.40; 36.80)	36.60 (36.50; 36.80)	36.60 (36.50; 36.80)
min max	35.7 39.1	35.0 38.6	35.0 39.1
first GCS on arrival			
n	508	533	1041
Mean (SD)	11.7 (2.66)	11.7 (2.90)	11.7 (2.78)
Median (Q1; Q3)	12.0 (10.0; 14.0)	13.0 (10.0; 14.0)	12.0 (10.0; 14.0)
min max	3 15	3 15	3 15
first NIHSS on arrival			
n	527	546	1073
Mean (SD)	16.1 (7.90)	16.0 (7.79)	16.1 (7.84)
Median (Q1; Q3)	15.0 (10.0; 21.0)	15.0 (10.0; 20.0)	15.0 (10.0; 20.0)
min max	0 42	1 42	0 42

Characteristics	FYTF-919 (N = 528)	Placebo (N = 551)	Overall (N = 1079)
NIHSS category			
NIHSS >=15	292/527 (55.4%)	295/546 (54.0%)	587/1073 (54.7%)
NIHSS < 15	235/527 (44.6%)	251/546 (46.0%)	486/1073 (45.3%)
Time from onset to arrival (hour)			
n	528	551	1079
Mean (SD)	5.5 (6.95)	5.0 (6.08)	5.3 (6.52)
Median (Q1; Q3)	3.1 (2.0; 5.7)	3.0 (1.9; 5.2)	3.0 (1.9; 5.4)
min max	0 55	0 46	0 55
Time from onset to randomization (hour)			
n	528	551	1079
Mean (SD)	18.2 (13.06)	18.0 (12.17)	18.1 (12.61)
Median (Q1; Q3)	14.9 (7.5; 25.7)	15.5 (7.7; 25.5)	15.2 (7.6; 25.6)
min max	2 81	1 69	1 81
Time from onset to first medicine given (hour)			
n	520	548	1068
Mean (SD)	23.0 (14.55)	22.3 (13.31)	22.6 (13.93)
Median (Q1; Q3)	20.0 (11.5; 31.0)	19.9 (12.0; 29.2)	20.0 (11.8; 30.3)
min max	2 109	2 84	2 109
First IMP method			
Oral admission（awake，33ml/time，tid）	261/518 (50.4%)	279/548 (50.9%)	540/1066 (50.7%)

Characteristics	FYTF-919 (N = 528)	Placebo (N = 551)	Overall (N = 1079)
Nasogastric tube（coma，25ml/time, q6h）	257/518 (49.6%)	269/548 (49.1%)	526/1066 (49.3%)
Previous Hypertension	342/526 (65.0%)	363/550 (66.0%)	705/1076 (65.5%)
Antihypertensive medication	321/342 (93.9%)	343/363 (94.5%)	664/705 (94.2%)
ACEI ARB	21/321 (6.5%)	27/343 (7.9%)	48/664 (7.2%)
Beta blocker	8/321 (2.5%)	9/343 (2.6%)	17/664 (2.6%)
Ca antagonist	51/321 (15.9%)	63/343 (18.4%)	114/664 (17.2%)
Diuretics	1/321 (0.3%)	3/343 (0.9%)	4/664 (0.6%)
Other antihypertensives	246/321 (76.6%)	254/343 (74.1%)	500/664 (75.3%)
Reserpine Co	2/246 (0.8%)	2/254 (0.8%)	4/500 (0.8%)
Unknown	244/246 (99.2%)	252/254 (99.2%)	496/500 (99.2%)
Previous Diabetes	43/528 (8.1%)	44/550 (8.0%)	87/1078 (8.1%)
Antidiabetic medication	14/43 (32.6%)	21/44 (47.7%)	35/87 (40.2%)
Insulin	1/14 (7.1%)	0/21 (0.0%)	1/35 (2.9%)

Characteristics	FYTF-919 (N = 528)	Placebo (N = 551)	Overall (N = 1079)
Biguanide	2/14 (14.3%)	1/21 (4.8%)	3/35 (8.6%)
Sulfonylurea	0/14 (0.0%)	0/21 (0.0%)	0/35 (0.0%)
Glycosidase inhibitor	1/14 (7.1%)	0/21 (0.0%)	1/35 (2.9%)
Other	12/14 (85.7%)	20/21 (95.2%)	32/35 (91.4%)
Euphridine	1/12 (8.3%)	0/20 (0.0%)	1/32 (3.1%)
Unknown	11/12 (91.7%)	20/20 (100.0%)	31/32 (96.9%)
Previous Hyperlipidemia	10/528 (1.9%)	6/551 (1.1%)	16/1079 (1.5%)
Lipid lowering agent	8/10 (80.0%)	4/6 (66.7%)	12/16 (75.0%)
Statin	5/8 (62.5%)	1/4 (25.0%)	6/12 (50.0%)
Cholesterol absorption inhibitor	0/8 (0.0%)	0/4 (0.0%)	0/12 (0.0%)
PCSK9 inhibitor	0/8 (0.0%)	0/4 (0.0%)	0/12 (0.0%)
Other (All unknown)	3/8 (37.5%)	3/4 (75.0%)	6/12 (50.0%)
Previous Coronary Heart Disease	23/528 (4.4%)	10/551 (1.8%)	33/1079 (3.1%)
Previous Atrial Fibrillation	1/528 (0.2%)	3/551 (0.5%)	4/1079 (0.4%)

Characteristics	FYTF-919 (N = 528)	Placebo (N = 551)	Overall (N = 1079)
Any anticoagular treatment	1/528 (0.2%)	1/551 (0.2%)	2/1079 (0.2%)
Any antiplatelet treatment	23/528 (4.4%)	18/551 (3.3%)	41/1079 (3.8%)
Aspirin	20/23 (87.0%)	16/18 (88.9%)	36/41 (87.8%)
Clopidogrel	5/23 (21.7%)	5/18 (27.8%)	10/41 (24.4%)
Other	1/23 (4.3%)	1/18 (5.6%)	2/41 (4.9%)
Total TCM score (TCM 1-5)			
n	508	528	1036
Mean (SD)	1.2 (1.29)	1.2 (1.28)	1.2 (1.29)
Median (Q1; Q3)	1.0 (0.0; 2.0)	1.0 (0.0; 2.0)	1.0 (0.0; 2.0)
min max	0 5	0 5	0 5
Anxiety	73/507 (14.4%)	66/528 (12.5%)	139/1035 (13.4%)
Red face/T>37.5	110/507 (21.7%)	111/527 (21.1%)	221/1034 (21.4%)
Dry mouth/Bad breath	124/502 (24.7%)	138/524 (26.3%)	262/1026 (25.5%)
Yellow tongue coating	129/495 (26.1%)	133/517 (25.7%)	262/1012 (25.9%)
Red tongue coating	182/495 (36.8%)	184/516 (35.7%)	366/1011 (36.2%)

Characteristics	FYTF-919 (N = 528)	Placebo (N = 551)	Overall (N = 1079)
No Stool in the last 48h	161/509 (31.6%)	181/527 (34.3%)	342/1036 (33.0%)

Table S9. Adherence to study medication

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N = 1641)
Median time to first does of study medication	20.0 (11.3-31.5)	20.0 (11.5-29.4)	20.0 (11.4-30.5)
Route of administration of first dose of study medication			
Oral	400/803 (49.8)	403/821 (49.1)	803/1624 (49.4)
Nasogastric tube	403/803 (50.2)	418/821 (50.9)	821/1624 (50.6)
Duration of study treatment, days			
n	804	821	1625
Mean (SD)	24.9 (10.2)	25.3 (9.2)	25.1 (9.7)
Median (Q1; Q3)	29.0 (26.0; 29.0)	29.0 (27.0; 29.0)	29.0 (27.0; 29.0)
min max	1 108	1 103	1 108
Duration of study treatment by category			
1 - 7 days	76/804 (9.5)	68/821 (8.3)	144/1625 (8.9)
8 - 14 days	70/804 (8.7)	56/821 (6.8)	126/1625 (7.7)
15 - 21 days	31/804 (3.9)	42/821 (5.1)	73/1625 (4.5)
22 - 28 days	177/804 (22.0)	169/821 (20.6)	346/1625 (21.3)
29 - 40 days	445/804 (55.3)	475/821 (57.9)	920/1625 (56.6)
40+ days	5/804 (0.6)	11/821 (1.3)	16/1625 (1.0)
Bottles completed			
Mean (SD)	22.8 (9.1)	23.5 (8.5)	23.2 (8.8)
Median (Q1; Q3)	28.0 (21.3; 28.0)	28.0 (25.0; 28.0)	28.0 (24.0; 28.0)
min max	0 28	0 28	0 28
Complete ≥80% of medication in all participants*	608/815 (74.6)	634/826 (76.8)	1242/1641 (75.7)
Completed study medication according to protocol in all participants†	491/815 (60.2)	503/826 (60.9)	994/1641 (60.6)
Complete ≥80% of medication in survivors	605/742 (81.5)	630/756 (83.3)	1235/1498 (82.4)

Data are n (%), mean (SD) or median (IQR), *Finished all study medication, †Finished 28 bottles in 28 days

Table S10. Details of the management of patients with acute intracerebral haemorrhage

Characteristic	FYTF-919 (N=815)	Placebo (N=826)	Overall (N = 1641)
ICU care			
Baseline	562/815 (69.0)	574/825 (69.6)	1136/1640 (69.3)
Follow up 1 - 24h(±3h)	470/813 (57.8)	489/825 (59.3)	959/1638 (58.5)
Follow up 2 - D7±D1	243/801 (30.3)	300/812 (36.9)	543/1613 (33.7)
Follow up 3 - D14±D2	116/749 (15.5)	147/775 (19.0)	263/1524 (17.3)
Follow up 4 - D28±D3	55/711 (7.7)	64/725 (8.8)	119/1436 (8.3)
Surgery			
Baseline	288/815 (35.3)	276/825 (33.5)	564/1640 (34.4)
Follow up 1 - 24h(±3h)	103/813 (12.7)	109/825 (13.2)	212/1638 (12.9)
Follow up 2 - D7±D1	27/801 (3.4)	25/812 (3.1)	52/1613 (3.2)
Follow up 3 - D14±D2	4/749 (0.5)	2/775 (0.3)	6/1524 (0.4)
Follow up 4 - D28±D3	2/711 (0.3)	4/725 (0.6)	6/1436 (0.4)
Tracheal intubation ± tracheotomy			
Baseline	139/815 (17.1)	150/825 (18.2)	289/1640 (17.6)
Follow up 1 - 24h(±3h)	157/813 (19.3)	166/825 (20.1)	323/1638 (19.7)
Follow up 2 - D7±D1	133/801 (16.6)	170/812 (20.9)	303/1613 (18.8)
Follow up 3 - D14±D2	73/748 (9.8)	102/775 (13.2)	175/1523 (11.5)
Follow up 4 - D28±D3	37/711 (5.2)	67/724 (9.3)	104/1435 (7.2)
Mechanical ventilation			
Baseline	125/815 (15.3)	141/825 (17.1)	266/1640 (16.2)
Follow up 1 - 24h(±3h)	131/813 (16.1)	139/825 (16.8)	270/1638 (16.5)
Follow up 2 - D7±D1	104/801 (13.0)	121/812 (14.9)	225/1613 (13.9)
Follow up 3 - D14±D2	46/748 (6.1)	61/775 (7.9)	107/1523 (7.0)
Follow up 4 - D28±D3	15/711 (2.1)	26/724 (3.6)	41/1435 (2.9)
Physical or drug hypothermia			
Baseline	111/815 (13.6)	109/825 (13.2)	220/1640 (13.4)
Follow up 1 - 24h(±3h)	154/813 (18.9)	175/825 (21.2)	329/1638 (20.1)
Follow up 2 - D7±D1	182/801 (22.7)	216/812 (26.6)	398/1613 (24.7)
Follow up 3 - D14±D2	101/749 (13.5)	126/775 (16.3)	227/1524 (14.9)
Follow up 4 - D28±D3	29/711 (4.1)	43/724 (5.9)	72/1435 (5.0)
Nasogastric feeding			
Baseline	396/815 (48.6)	418/825 (50.7)	814/1640 (49.6)
Follow up 1 - 24h(±3h)	439/813 (54.0)	448/825 (54.3)	887/1638 (54.2)
Follow up 2 - D7±D1	393/801 (49.1)	410/812 (50.5)	803/1613 (49.8)
Follow up 3 - D14±D2	288/749 (38.5)	310/775 (40.0)	598/1524 (39.2)
Follow up 4 - D28±D3	158/711 (22.2)	175/724 (24.2)	333/1435 (23.2)

Characteristic	FYTF-919 (N=815)	Placebo (N=826)	Overall (N = 1641)
Urinary catheterisation			
Baseline	543/815 (66.6)	560/825 (67.9)	1103/1640 (67.3)
Follow up 1 - 24h(±3h)	539/813 (66.3)	554/825 (67.2)	1093/1638 (66.7)
Follow up 2 - D7±D1	463/801 (57.8)	473/812 (58.3)	936/1613 (58.0)
Follow up 3 - D14±D2	292/749 (39.0)	316/775 (40.8)	608/1524 (39.9)
Follow up 4 - D28±D3	142/711 (20.0)	163/724 (22.5)	305/1435 (21.3)
Other invasive treatment			
Baseline	80/815 (9.8)	93/825 (11.3)	173/1640 (10.5)
Follow up 1 - 24h(±3h)	77/813 (9.5)	84/825 (10.2)	161/1638 (9.8)
Follow up 2 - D7±D1	165/801 (20.6)	176/812 (21.7)	341/1613 (21.1)
Follow up 3 - D14±D2	89/749 (11.9)	119/775 (15.4)	208/1524 (13.6)
Follow up 4 - D28±D3	31/711 (4.4)	37/724 (5.1)	68/1435 (4.7)
Physical or drug hypothermia			
Baseline	111/815 (13.6)	109/825 (13.2)	220/1640 (13.4)
Follow up 1 - 24h(±3h)	154/813 (18.9)	175/825 (21.2)	329/1638 (20.1)
Follow up 2 - D7±D1	182/801 (22.7)	216/812 (26.6)	398/1613 (24.7)
Follow up 3 - D14±D2	101/749 (13.5)	126/775 (16.3)	227/1524 (14.9)
Follow up 4 - D28±D3	29/711 (4.1)	43/724 (5.9)	72/1435 (5.0)
Analgesia and sedation			
Baseline	317/814 (38.9)	338/824 (41.0)	655/1638 (40.0)
Follow up 1 - 24h(±3h)	299/812 (36.8)	331/825 (40.1)	630/1637 (38.5)
Follow up 2 - D7±D1	225/800 (28.1)	257/811 (31.7)	482/1611 (29.9)
Follow up 3 - D14±D2	110/748 (14.7)	131/775 (16.9)	241/1523 (15.8)
Follow up 4 - D28±D3	48/710 (6.8)	47/724 (6.5)	95/1434 (6.6)
Proton pump inhibitor use			
Baseline	594/815 (72.9)	612/825 (74.2)	1206/1640 (73.5)
Follow up 1 - 24h(±3h)	577/813 (71.0)	597/825 (72.4)	1174/1638 (71.7)
Follow up 2 - D7±D1	486/801 (60.7)	485/812 (59.7)	971/1613 (60.2)
Follow up 3 - D14±D2	279/749 (37.2)	276/775 (35.6)	555/1524 (36.4)
Follow up 4 - D28±D3	122/710 (17.2)	113/724 (15.6)	235/1434 (16.4)
Diuretic use			
Baseline	105/815 (12.9)	90/825 (10.9)	195/1640 (11.9)
Follow up 1 - 24h(±3h)	116/813 (14.3)	123/825 (14.9)	239/1638 (14.6)
Follow up 2 - D7±D1	153/801 (19.1)	176/812 (21.7)	329/1613 (20.4)
Follow up 3 - D14±D2	104/749 (13.9)	113/775 (14.6)	217/1524 (14.2)
Follow up 4 - D28±D3	32/710 (4.5)	61/724 (8.4)	93/1434 (6.5)
Anti-epilepsy drug use			

Characteristic	FYTF-919 (N=815)	Placebo (N=826)	Overall (N = 1641)
Baseline	169/815 (20.7)	170/825 (20.6)	339/1640 (20.7)
Follow up 1 - 24h(±3h)	155/813 (19.1)	171/825 (20.7)	326/1638 (19.9)
Follow up 2 - D7±D1	130/801 (16.2)	149/812 (18.3)	279/1613 (17.3)
Follow up 3 - D14±D2	88/749 (11.7)	100/775 (12.9)	188/1524 (12.3)
Follow up 4 - D28±D3	39/710 (5.5)	56/724 (7.7)	95/1434 (6.6)
Dehydration therapy			
Baseline	531/815 (65.2)	563/825 (68.2)	1094/1640 (66.7)
Follow up 1 - 24h(±3h)	547/813 (67.3)	585/825 (70.9)	1132/1638 (69.1)
Follow up 2 - D7±D1	561/801 (70.0)	565/812 (69.6)	1126/1613 (69.8)
Follow up 3 - D14±D2	379/749 (50.6)	374/775 (48.3)	753/1524 (49.4)
Follow up 4 - D28±D3	97/710 (13.7)	96/724 (13.3)	193/1434 (13.5)
BP control			
Baseline	746/815 (91.5)	737/825 (89.3)	1483/1640 (90.4)
Follow up 1 - 24h(±3h)	732/813 (90.0)	718/825 (87.0)	1450/1638 (88.5)
Follow up 2 - D7±D1	730/801 (91.1)	724/812 (89.2)	1454/1613 (90.1)
Follow up 3 - D14±D2	643/749 (85.8)	652/775 (84.1)	1295/1524 (85.0)
Follow up 4 - D28±D3	548/711 (77.1)	550/724 (76.0)	1098/1435 (76.5)
Glucose control			
Baseline	74/815 (9.1)	85/825 (10.3)	159/1640 (9.7)
Follow up 1 - 24h(±3h)	90/813 (11.1)	105/825 (12.7)	195/1638 (11.9)
Follow up 2 - D7±D1	106/801 (13.2)	114/812 (14.0)	220/1613 (13.6)
Follow up 3 - D14±D2	78/749 (10.4)	99/775 (12.8)	177/1524 (11.6)
Follow up 4 - D28±D3	65/710 (9.2)	70/724 (9.7)	135/1434 (9.4)
Use of drugs to increase BP			
Baseline	7/815 (0.9)	6/825 (0.7)	13/1640 (0.8)
Follow up 1 - 24h(±3h)	11/813 (1.4)	9/825 (1.1)	20/1638 (1.2)
Follow up 2 - D7±D1	10/801 (1.2)	10/812 (1.2)	20/1613 (1.2)
Follow up 3 - D14±D2	9/749 (1.2)	6/775 (0.8)	15/1524 (1.0)
Follow up 4 - D28±D3	3/710 (0.4)	5/725 (0.7)	8/1435 (0.6)
Anticoagulation reversal			
Baseline	33/815 (4.0)	31/825 (3.8)	64/1640 (3.9)
Follow up 1 - 24h(±3h)	15/813 (1.8)	18/825 (2.2)	33/1638 (2.0)
Follow up 2 - D7±D1	11/801 (1.4)	6/812 (0.7)	17/1613 (1.1)
Follow up 3 - D14±D2	8/749 (1.1)	7/775 (0.9)	15/1524 (1.0)
Follow up 4 - D28±D3	2/710 (0.3)	2/724 (0.3)	4/1434 (0.3)
Rehabilitation			
Baseline	189/815 (23.2)	196/825 (23.8)	385/1640 (23.5)

Characteristic	FYTF-919 (N=815)	Placebo (N=826)	Overall (N = 1641)
Follow up 1 - 24h(±3h)	235/813 (28.9)	262/825 (31.8)	497/1638 (30.3)
Follow up 2 - D7±D1	372/801 (46.4)	390/813 (48.0)	762/1614 (47.2)
Follow up 3 - D14±D2	355/749 (47.4)	383/775 (49.4)	738/1524 (48.4)
Follow up 4 - D28±D3	251/711 (35.3)	275/725 (37.9)	526/1436 (36.6)
Acupuncture			
Baseline	72/815 (8.8)	79/825 (9.6)	151/1640 (9.2)
Follow up 1 - 24h(±3h)	105/813 (12.9)	124/825 (15.0)	229/1638 (14.0)
Follow up 2 - D7±D1	307/801 (38.3)	303/813 (37.3)	610/1614 (37.8)
Follow up 3 - D14±D2	334/749 (44.6)	332/775 (42.8)	666/1524 (43.7)
Follow up 4 - D28±D3	196/711 (27.6)	218/725 (30.1)	414/1436 (28.8)

Data are n (%)

BP denotes blood pressure, D day, ICU intensive care unit

Table S11. Clinical assessment of outcomes over time

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
NIHSS			
Baseline			
n	811	818	1629
Mean (SD)	16.2 (8.0)	16.3 (8.1)	16.3 (8.1)
Median (Q1; Q3)	15 (10-21)	15 (10-20)	15 (10-20)
min max	0 42	1 42	0 42
Follow up 1 - 24h(±3h)			
n	778	796	1574
Mean (SD)	16.1 (8.3)	16.4 (8.6)	16.3 (8.4)
Median (Q1; Q3)	15.0 (10.-21)	15.0 (10-21)	15.0 (10-21)
min max	0 42	0 41	0 42
Follow up 2 - D7±D1			
n	767	776	1543
Mean (SD)	13.3 (8.3)	13.8 (8.6)	13.6 (8.5)
Median (Q1; Q3)	12 (8-18)	12 (7-19)	12 (8-18)
min max	0 42	0 40	0 42
Follow up 3 - D14±D2			
n	684	704	1388
Mean (SD)	10.9 (7.7)	11.6 (8.1)	11.3 (7.9)
Median (Q1; Q3)	10 (5-15)	10.0 (6-15)	10.0 (6-15)
min max	0 42	0 41	0 42
Follow up 4 - D28±D3			
n	544	555	1099
Mean (SD)	8.3 (7.2)	9.0 (7.5)	8.7 (7.4)
Median (Q1; Q3)	7 (3-12)	7 (4-12)	7 (3-12)
min max	0 42	0 42	0 42
GCS			
Baseline			
n	784	791	1575
Mean (SD)	11.6 (2.8)	11.6 (3.0)	11.6 (2.9)
Median (Q1; Q3)	12 (10-14)	12 (10-14)	12 (10-14)
min max	3 15	3 15	3 15
Follow up 1 - 24h(±3h)			
n	758	761	1519

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Mean (SD)	11.6 (3.0)	11.6 (3.1)	11.6 (3.0)
Median (Q1; Q3)	12 (10-14)	13 (9-14)	12 (10-14)
min max	2 15	3 15	2 15
Follow up 2 - D7±D1			
n	735	729	1464
Mean (SD)	12.8 (2.7)	12.7 (2.9)	12.7 (2.8)
Median (Q1; Q3)	14 (11-15)	14 (11-15)	14 (11-15)
min max	3 15	3 15	3 15
Follow up 3 - D14±D2			
n	680	686	1366
Mean (SD)	13.5 (2.3)	13.3 (2.6)	13.4 (2.5)
Median (Q1; Q3)	15 (12-15)	15 (12-15)	15 (12-15)
min max	3 15	2 15	2 15
Follow up 4 - D28±D3			
n	598	611	1209
Mean (SD)	14.1 (1.8)	14.0 (2.1)	14.1 (2.0)
Median (Q1; Q3)	15 (14-15)	15 (14-15)	15 (14.-15)
min max	5 15	3 15	3 15
mRS			
Baseline (before stroke onset)			
0: No symptoms	738/814 (90.7)	747/826 (90.4)	1485/1640 (90.5)
1: No significant disability	47/814 (5.8)	43/826 (5.2)	90/1640 (5.5)
2: Slight disability	29/814 (3.6)	36/826 (4.4)	65/1640 (4.0)
3: Moderate disability	0/814 (0.0)	0/826 (0.0)	0/1640 (0.0)
4: Moderately severe disability	0/814 (0.0)	0/826 (0.0)	0/1640 (0.0)
5: Severe disability	0/814 (0.0)	0/826 (0.0)	0/1640 (0.0)
6: Death	0/814 (0.0)	0/826 (0.0)	0/1640 (0.0)
Follow up 4 - D28±D3			
0: No symptoms	28/787 (3.6)	33/800 (4.1)	61/1587 (3.8)
1: No significant disability	126/787 (16.0)	106/800 (13.3)	232/1587 (14.6)
2: Slight disability	96/787 (12.2)	97/800 (12.1)	193/1587 (12.2)
3: Moderate disability	104/787 (13.2)	116/800 (14.5)	220/1587 (13.9)
4: Moderately severe disability	294/787 (37.4)	283/800 (35.4)	577/1587 (36.4)
5: Severe disability	66/787 (8.4)	95/800 (11.9)	161/1587 (10.1)
6: Death	73/787 (9.3%)	70/800 (8.8%)	143/1587 (9.0%)
Follow up 5 - D90±D7			
0: No symptoms	61/801 (7.6)	60/818 (7.3)	121/1619 (7.5)

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
1: No significant disability	159/801 (19.9)	158/818 (19.3)	317/1619 (19.6)
2: Slight disability	122/801 (15.2)	127/818 (15.5)	249/1619 (15.4)
3: Moderate disability	153/801 (19.1)	162/818 (19.8)	315/1619 (19.5)
4: Moderately severe disability	178/801 (22.2)	169/818 (20.7)	347/1619 (21.4)
5: Severe disability	30/801 (3.7)	49/818 (6.0)	79/1619 (4.9)
6: Death	98/801 (12.2)	93/818 (11.4)	191/1619 (11.8)
Barthel index			
Follow up 4 - D28±D3			
n	711	729	1440
Mean (SD)	56.1 (32.5)	54.1 (33.0)	55.1 (32.8)
Median (Q1; Q3)	55 (25-90)	55 (25-85)	55 (25-88)
min max	0 100	0 100	0 100
Follow up 5 - D90±D7			
n	704	728	1432
Mean (SD)	71.2 (29.2)	69.7 (29.8)	70.4 (29.5)
Median (Q1; Q3)	80 (50-100)	80.(50-95)	80 (50-100)
min max	0 100	0 100	0 100
EQ-5D-5L VAS			
Follow up 4 - D28±D3			
n	702	723	1425
Mean (SD)	63.0 (24.4)	62.4 (24.9)	62.7 (24.7)
Median (Q1; Q3)	67 (50-80)	65 (50-80)	65 (50-80)
min max	0 100	0 100	0 100
Follow up 5 - D90±D7			
n	704	728	1432
Mean (SD)	71.9 (22.3)	71.3 (22.3)	71.6 (22.3)
Median (Q1; Q3)	79 (60-90)	80 (60-90)	80 (60-90)
min max	0 100	0 100	0 100
EQ-5D-5L Utility score in survivors			
Follow up 4 - D28±D3			
n	703	721	1424
Mean (SD)	0.42 (0.42)	0.41 (0.41)	0.41 (0.41)
Median (Q1; Q3)	0.38 (0.06; 0.83)	0.36 (0.06; 0.79)	0.36 (0.06; 0.81)
min max	-0.39 1.00	-0.39 1.00	-0.39 1.00
Follow up 5 - D90±D7			
n	703	725	1428

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Mean (SD)	0.58 (0.40)	0.58 (0.38)	0.58 (0.39)
Median (Q1; Q3)	0.73 (0.22; 0.94)	0.72 (0.22; 0.93)	0.73 (0.22; 0.93)
min max	-0.39 1.00	-0.39 1.00	-0.39 1.00
EQ-5D-5L Utility score imputing Death as zero			
Follow up 4 - D28±D3			
n	776	791	1567
Mean (SD)	0.38 (0.41)	0.374 (0.41)	0.38 (0.41)
Median (Q1; Q3)	0.22 (0.00; 0.78)	0.23 (0.00; 0.78)	0.22 (0.00; 0.78)
min max	-0.39 1.00	-0.39 1.00	-0.39 1.00
Follow up 5 - D90±D7			
n	801	818	1619
Mean (SD)	0.51 (0.42)	0.52 (0.40)	0.51 (0.41)
Median (Q1; Q3)	0.62 (0.10; 0.89)	0.58 (0.12; 0.89)	0.62 (0.11; 0.89)
min max	-0.39 1.00	-0.39 1.00	-0.39 1.00

Data are n (%), mean (SD) or median (IQR)

Table S12. Haematoma volumes and presence of intraventricular haemorrhage over time

	FYTF-919 (N=815)	Placebo (N=826)	Overall (N = 1641)
Haematoma, ml			
Baseline			
n	775	792	1567
Mean (SD)	24.6 (22.76)	23.2 (21.85)	23.9 (22.31)
Median (Q1; Q3)	18.0 (8.0; 35.0)	16.9 (8.1; 30.0)	17.6 (8.0; 32.0)
min max	0 182	0 181	0 182
24 h			
n	491	513	1004
Mean (SD)	17.5 (17.19)	17.0 (15.44)	17.3 (16.31)
Median (Q1; Q3)	11.8 (5.9; 23.9)	12.0 (6.6; 22.5)	12.0 (6.1; 23.2)
min max	0 110	0 99	0 110
Day 7			
n	494	507	1001
Mean (SD)	10.8 (11.19)	10.2 (10.00)	10.5 (10.60)
Median (Q1; Q3)	7.3 (3.6; 14.5)	7.3 (4.0; 13.0)	7.3 (4.0; 13.8)
min max	0 78	0 78	0 78
Day 14			
n	297	313	610
Mean (SD)	7.0 (13.62)	5.6 (6.75)	6.3 (10.68)
Median (Q1; Q3)	4.0 (1.5; 8.3)	3.0 (1.2; 7.4)	3.5 (1.4; 7.9)
min max	0 191	0 41	0 191
Intraventricular haemorrhage			
Baseline			
No	450/809 (55.6)	489/821 (59.6)	939/1630 (57.6)
Yes	359/809 (44.4)	332/821 (40.4)	691/1630 (42.4)
24 h			
No	320/625 (51.2)	369/645 (57.2)	689/1270 (54.3)
Yes	305/625 (48.8)	276/645 (42.8)	581/1270 (45.7)
Day 7			
No	413/695 (59.4)	442/704 (62.8)	855/1399 (61.1)
Yes	282/695 (40.6)	262/704 (37.2)	544/1399 (38.9)
Day14			
No	358/499 (71.7)	392/527 (74.4)	750/1026 (73.1)
Yes	141/499 (28.3)	135/527 (25.6)	276/1026 (26.9)

Data are n (%), mean (SD) or median (IQR)

Table S13. Method of assessment of the 90 day outcome

Method	**FYTF-919 (N=815)**	**Placebo (N=826)**	**Overall (N = 1641)**
Outpatient clinic	40/724 (5.5)	29/742 (3.9)	69/1466 (4.7)
Home visit	10/724 (1.4)	9/742 (1.2)	19/1466 (1.3)
Remote	666/724 (92.0)	688/742 (92.7)	1354/1466 (92.4)
Other	8/724 (1.1)	16/742 (2.2)	24/1466 (1.6)

Table S14. Descriptive analysis of EQ-5D-5L at Day 90

Outcome	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Mobility			
1: I have no problems with walking about	237/704 (33.7)	244/729 (33.5)	481/1433 (33.6)
2: I have slight problems with walking about	158/704 (22.4)	167/729 (22.9)	325/1433 (22.7)
3: I have moderate problems with walking about	96/704 (13.6)	108/729 (14.8)	204/1433 (14.2)
4: I have severe problems with walking about	66/704 (9.4)	65/729 (8.9)	131/1433 (9.1)
5: I am unable to walk about	147/704 (20.9)	145/729 (19.9)	292/1433 (20.4)
Self care			
1: I have no problems with washing or dressing myself	230/704 (32.7)	238/729 (32.6)	468/1433 (32.7)
2: I have slight problems with washing or dressing myself	147/704 (20.9)	134/729 (18.4)	281/1433 (19.6)
3: I have moderate problems with washing or dressing myself	101/704 (14.3)	113/729 (15.5)	214/1433 (14.9)
4: I have severe problems with washing or dressing myself	79/704 (11.2)	83/729 (11.4)	162/1433 (11.3)
5: I am unable to wash or dress myself	147/704 (20.9)	161/729 (22.1)	308/1433 (21.5)
Usual activities			
1: I have no problems doing my usual activities	214/704 (30.4)	222/729 (30.5)	436/1433 (30.4)
2: I have slight problems doing my usual activities	174/704 (24.7)	158/729 (21.7)	332/1433 (23.2)
3: I have moderate problems doing my usual activities	110/704 (15.6)	131/729 (18.0)	241/1433 (16.8)
4: I have severe problems doing my usual activities	95/704 (13.5)	102/729 (14.0)	197/1433 (13.7)
5: I am unable to do my usual activities	111/704 (15.8)	116/729 (15.9)	227/1433 (15.8)
Pain / discomfort			
1: I have no pain of discomfort	375/704 (53.3)	393/729 (53.9)	768/1433 (53.6)
2: I have slight pain of discomfort	231/704 (32.8)	240/729 (32.9)	471/1433 (32.9)

Outcome	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
3: I have moderate pain of discomfort	62/704 (8.8)	52/729 (7.1)	114/1433 (8.0)
4: I have severe pain of discomfort	13/704 (1.8)	26/729 (3.6)	39/1433 (2.7)
5: I am extreme pain of discomfort	23/704 (3.3)	18/729 (2.5)	41/1433 (2.9)
Anxiety / depression			
1: I am not anxious or depressed	339/704 (48.2)	355/729 (48.7)	694/1433 (48.4)
2: I am slightly anxious or depressed	245/704 (34.8)	242/729 (33.2)	487/1433 (34.0)
3: I am moderately anxious or depressed	74/704 (10.5)	93/729 (12.8)	167/1433 (11.7)
4: I am severely anxious or depressed	23/704 (3.3)	24/729 (3.3)	47/1433 (3.3)
5: I am extremely anxious or depressed	23/704 (3.3)	15/729 (2.1)	38/1433 (2.7)
VAS 0-100*			
n	704	728	1432
Mean (SD)	71.9 (22.31)	71.3 (22.28)	71.6 (22.29)
Median (Q1; Q3)	79.0 (60.0; 90.0)	80.0 (60.0; 90.0)	80.0 (60.0; 90.0)
min max	0 100	0 100	0 100

Data are n (%), mean (SD) or median (IQR)

*VAS denotes visual analogue scale

Table S15. Description of the clinical outcomes at 28 and 90 days*

	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Utility weighted mRS at Day 90			
n	801	818	1619
Mean (SD)	0.50 (0.35)	0.50 (0.36)	0.50 (0.36)
Median (Q1; Q3)	0.55 (0.20; 0.88)	0.55 (0.20; 0.88)	0.55 (0.20; 0.88)
min max	-0.19 0.97	-0.19 0.97	-0.19 0.97
Death or disability (mRS 4-6) at Day 28	433/787 (55.0)	448/800 (56.0)	881/1587 (55.5)
Death or disability (mRS 4-6) at Day 90	306/801 (38.2)	311/818 (38.0)	617/1619 (38.1)
Death at Day 28	73/815 (9.0)	70/825 (8.5)	143/1640 (8.7)
Death at Day 90	98/815 (12.0)	93/826 (11.3)	191/1641 (11.6)
Disability (mRS 4-5) at Day 28	360/787 (45.7)	378/800 (47.3)	738/1587 (46.5)
Disability (mRS 4-5) at Day 90	208/801 (26.0)	218/818 (26.7)	426/1619 (26.3)
Stroke associated pneumonia (SAP)	31/764 (4.1)	30/779 (3.9)	61/1543 (4.0)
Hospital discharge by Day 28	610/751 (81.2)	627/775 (8039)	1237/1526 (81.1)
Hospital discharge alive by Day 28 and remain alive within 7 days	607/748 (81.1)	624/772 (80.8)	1231/1520 (81.0)

Data are n (%), mean (SD) or median (IQR)

mRS indicates modified Rankin scale

Table S16. Sensitivity analysis of the primary outcome and analysis of the secondary outcomes at 28, 90 and 180 days

		Primary model (1)			Adjusted model (2)	
Outcome	**N***	**OR/MD (95%CI)****	**p value**	**N***	**OR/MD (95%CI)****	**p value**
Primary Outcome						
uwMRS Day 90	1577	0.008 (-0.02, 0.04)	0.63	1576	0.015 (-0.02, 0.04)	0.33
uwMRS Day 90 - sensitivity 1	1577	0.004 (-0.03, 0.04)	0.80			
uwMRS Day 90 - sensitivity 2	1397	0.005 (-0.03, 0.04)	0.78			
uwMRS Day 90 - sensitivity 3	1577	0.004 (-0.03, 0.04)	0.80			
Secondary Outcomes						
uwMRS Day 180	1596	-0.003 (-0.03, 0.03)	0.88	1595	0.005 (-0.03, 0.04)	0.75
Ordinal mRS Day 28**	1551	0.89 (0.74, 1.06)	0.20	1550	0.86 (0.72, 1.03)	0.10
Ordinal mRS Day 90**	1577	1.00 (0.84, 1.20)	0.97	1576	0.97 (0.81, 1.15)	0.71
Ordinal mRS Day 180**	1596	1.01 (0.85, 1.20)	0.91	1595	0.98 (0.82, 1.16)	0.78
Death or disability - mRS [4-6] Day 28**	1551	0.94 (0.74, 1.19)	0.61	1550	0.91 (0.72, 1.15)	0.44
Death or disability - mRS [4-6] Day 90**	1577	1.01 (0.80, 1.26)	0.97	1576	0.94 (0.75, 1.19)	0.63
Death or disability – mRS [4-6] Day 180**	1596	1.04 (0.83, 1.31)	0.73	1595	0.97 (0.76, 1.24)	0.80
Death Day 28**	1597	1.03 (0.71, 1.48)	0.88	1596	0.95 (0.65, 1.39)	0.80
Death Day 90**	1597	1.06 (0.77, 1.46)	0.74	1596	0.98 (0.70, 1.38)	0.91
Death Day 180**	1597	1.02 (0.76, 1.38)	0.89	1596	0.95 (0.69, 1.30)	0.75
Disability - mRS [4-5] Day 28**	1551	0.93 (0.74, 1.16)	0.51	1550	0.92 (0.74, 1.16)	0.49
Disability - mRS [4-5] Day 90**	1577	0.97 (0.76, 1.23)	0.78	1576	0.95 (0.75, 1.21)	0.69
Disability – mRS [4-5] Day 180**	1596	1.03 (0.79, 1.35)	0.81	1595	1.01 (0.77, 1.33)	0.93
NIHSS Day 1	1541	-0.26 (-0.83, 0.31)	0.37	1540	-0.28 (-0.85, 0.29)	0.34

Outcome	Primary model (1) N*	Primary model (1) OR/MD (95%CI)**	Primary model (1) p value	Adjusted model (2) N*	Adjusted model (2) OR/MD (95%CI)**	Adjusted model (2) p value
NIHSS Day 7	1509	-0.54 (-1.21, 0.14)	0.12	1508	-0.59 (-1.26, 0.09)	0.09
Barthel Index Day 28	1411	1.74 (-0.17, 4.66)	0.24	1410	2.11 (-0.80, 5.01)	0.15
Barthel Index Day 90	1396	0.76 (-2.01, 3.53)	0.59	1395	1.28 (-1.43, 4.00)	0.35
Bathel Index Day 180	1382	-0.33 (-2.91, 2.26)	0.80	1381	0.21 (-2.28, 2.70)	0.87
EQ-5D-5L VAS in survivors Day 28	1321	0.15 (-2.10, 2.41)	0.89	1320	0.32 (-1.93, 2.58)	0.78
EQ-5D-5L VAS in survivors Day 90	1363	-0.55 (-2.60, 1.51)	0.60	1362	-0.34 (-2.39, 1.71)	0.75
EQ5D5L VAS in survivors Day 180	1378	-0.91 (-2.96, 1.15)	0.39	1377	-0.70 (-2.74, 1.34)	0.50
EQ-5D-5L Utility score in survivors Day 28	1323	0.00 (-0.03, 0.04)	0.88	1322	0.01 (-0.03, 0.04)	0.77
EQ-5D-5L Utility score in survivors Day 90	1363	-0.01 (-0.05, 0.02)	0.46	1362	-0.01 (-0.04, 0.03)	0.67
EQ5D5L Utility score in survivors Day 180	1378	-0.02 (-0.05, 0.02)	0.38	1377	-0.01 (-0.04, 0.02)	0.57
EQ-5D-5L VAS Day 28 (impute death = 0)	1532	0.22 (-2.40, 2.84)	0.87	1531	0.61 (-1.99, 3.20)	0.65
EQ-5D-5L VAS Day 90 (impute death = 0)	1576	-0.39 (-3.17, 2.38)	0.78	1575	0.13 (-2.57, 2.83)	0.93
EQ5D5L VAS Day 180 (impute death = 0)	1596	-0.59 (-3.52, 2.33)	0.69	1595	-0.06 (-2.88, 2.77)	0.97
EQ-5D-5L Utility score Day 28 (impute death = 0)	1536	0.01 (-0.03, 0.04)	0.68	1535	0.01 (-0.02, 0.05)	0.54
EQ-5D-5L Utility score Day 90 (impute death = 0)	1577	-0.00 (-0.04, 0.03)	0.71	1576	0.00 (-0.03, 0.04)	0.98
EQ5D5L Utility score Day 180 (impute death = 0)	1596	-0.01 (-0.05, 0.03)	0.59	1595	-0.00 (-0.04, 0.03)	0.91
Any pneumonia	1500	1.04 (0.560 1.80)	0.90	1500	1.02 (0.58, 1.78)	0.95

EQ-5D-5L denoted EuroQol health-related quality of life questionnaire, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, uw-mRS utility weighted modified Rankin scale, VAS visual analogue scale

Table S17. Outcomes in younger participants (age <65 years)

a. **Adherence to study medication**

Characteristics	FYTF-919 (N = 451)	Placebo (N = 494)	Overall (N = 945)
Duration of study treatment (Days)			
n	443	491	934
Mean (SD)	26.0 (10.11)	25.6 (8.35)	25.8 (9.23)
Median (Q1; Q3)	29.0 (28.0; 29.0)	29.0 (28.0; 29.0)	29.0 (28.0; 29.0)
min max	1 108	1 58	1 108
Duration of study treatment by category			
1 - 7 days	32/443 (7.2%)	34/491 (6.9%)	66/934 (7.1%)
8 - 14 days	29/443 (6.5%)	33/491 (6.7%)	62/934 (6.6%)
15 - 21 days	16/443 (3.6%)	23/491 (4.7%)	39/934 (4.2%)
22 - 28 days	104/443 (23.5%)	106/491 (21.6%)	210/934 (22.5%)
29 - 40 days	258/443 (58.2%)	290/491 (59.1%)	548/934 (58.7%)
40+ days	4/443 (0.9%)	5/491 (1.0%)	9/934 (1.0%)
Bottles completed			
n	451	494	945
Mean (SD)	23.7 (8.55)	23.9 (8.17)	23.8 (8.35)
Median (Q1; Q3)	28.0 (26.3; 28.0)	28.0 (27.0; 28.0)	28.0 (27.0; 28.0)
min max	0 28	0 28	0 28
Complete ≥80% of medication	355/451 (78.7%)	392/494 (79.4%)	747/945 (79.0%)
Complete study medication following protocol [1]	281/451 (62.3%)	315/494 (63.8%)	596/945 (63.1%)

Characteristics	FYTF-919 (N = 451)	Placebo (N = 494)	Overall (N = 945)

b. Clinical outcomes

	FYTF-919 (N = 451)	Placebo (N = 494)	Overall (N = 945)
Utility weighted mRS at Day 90			
n	440	489	929
Mean (SD)	0.554 (0.3344)	0.561 (0.3343)	0.558 (0.3342)
Median (Q1; Q3)	0.550 (0.200; 0.880)	0.550 (0.200; 0.880)	0.550 (0.200; 0.880)
min max	-0.19 0.97	-0.19 0.97	-0.19 0.97
Death or disability (mRS 4-6) at Day 28	240/433 (55.4%)	242/475 (50.9%)	482/908 (53.1%)
Death or disability (mRS 4-6) at Day 90	141/440 (32.0%)	148/489 (30.3%)	289/929 (31.1%)
Death at Day 28	29/451 (6.4%)	24/494 (4.9%)	53/945 (5.6%)
Death at Day 90	34/451 (7.5%)	28/494 (5.7%)	62/945 (6.6%)
Disability (mRS 4-5) at Day 28	211/433 (48.7%)	218/475 (45.9%)	429/908 (47.2%)
Disability (mRS 4-5) at Day 90	107/440 (24.3%)	120/489 (24.5%)	227/929 (24.4%)
Stroke associated pneumonia (SAP)	18/429 (4.2%)	20/476 (4.2%)	38/905 (4.2%)
Hospital discharge by Day 28	360/418 (86.1%)	393/470 (83.6%)	753/888 (84.8%)

Table S18. Outcomes in older participants (age ≥65 years)

Characteristics	FYTF-919 (N = 364)	Placebo (N = 332)	Overall (N = 696)
Duration of study treatment (Days)			
n	361	330	491
Mean (SD)	23.5 (10.07)	24.9 (10.39)	24.1 (10.24)
Median (Q1; Q3)	29.0 (17.0; 29.0)	29.0 (25.0; 29.0)	29.0 (21.0; 29.0)
min max	1 80	1 103	1 103
Duration of study treatment by category			
1 - 7 days	44/361 (12.2%)	34/330 (10.3%)	79/691 (11.3%)
8 - 14 days	41/361 (11.4%)	23/330 (7.0%)	64/691 (9.3%)
15 - 21 days	15/361 (4.2%)	19/330 (5.8%)	34/691 (4.9%)
22 - 28 days	73/361 (20.2%)	63/330 (19.1%)	136/691 (19.7%)
29 - 40 days	187/361 (51.8%)	185/330 (56.1%)	372/691 (53.8%)
40+ days	1/361 (0.3%)	6/330 (1.8%)	7/691 (1.0%)
Bottles completed			
n	364	332	696
Mean (SD)	21.8 (9.64)	22.8 (8.96)	22.3 (9.33)
Median (Q1; Q3)	28.0 (14.0; 28.0)	28.0 (20.6; 28.0)	28.0 (17.0; 28.0)
min max	0 28	0 28	0 28
Complete ≥80% of medication	253/364 (69.5%)	242/332 (72.9%)	495/696 (71.1%)
Complete study medication following protocol [1]	210/364 (57.7%)	188/332 (56.6%)	398/696 (57.2%)

c. Clinical outcome

	FYTF-919 (N = 364)	**Placebo (N = 332)**	**Overall (N = 696)**
Utility weighted mRS at Day 90			
n	361	329	690
Mean (SD)	0.442 (0.3614)	0.396 (0.3731)	0.420 (0.3675)
Median (Q1; Q3)	0.550 (0.200; 0.740)	0.550 (0.000; 0.740)	0.550 (0.000; 0.740)
min max	-0.19 0.97	-0.19 0.97	-0.19 0.97
Death or disability (mRS 4-6) at Day 28	193/354 (54.5%)	206/325 (63.4%)	399/679 (58.8%)
Death or disability (mRS 4-6) at Day 90	165/361 (45.7%)	163/329 (49.5%)	328/690 (47.5%)
Death at Day 28	44/364 (12.1%)	46/332 (13.9%)	90/696 (12.9%)
Death at Day 90	64/364 (17.6%)	65/332 (19.6%)	129/696 (18.5%)
Disability (mRS 4-5) at Day 28	149/354 (42.1%)	160/325 (49.2%)	309/679 (45.5%)
Disability (mRS 4-5) at Day 90	101/361 (28.0%)	98/329 (29.8%)	199/690 (28.8%)
Stroke associated pneumonia (SAP)	13/335 (3.9%)	10/303 (3.3%)	23/638 (3.6%)
Hospital discharge by Day 28	250/333 (75.1%)	234/305 (76.7%)	484/638 (75.9%)

Table S19. Outcomes in female participants

A Adherence to study medication

Characteristics	FYTF-919 (N = 287)	Placebo (N = 275)	Overall (N = 562)
Duration of study treatment (Days)			
n	284	273	557
Mean (SD)	25.8 (9.86)	24.9 (9.24)	25.4 (9.56)
Median (Q1; Q3)	29.0 (28.0; 29.0)	29.0 (27.0; 29.0)	29.0 (28.0; 29.0)
min max	1 100	1 50	1 100
Duration of study treatment by category			
1 - 7 days	21/284 (7.4%)	25/273 (9.2%)	46/557 (8.3%)
8 - 14 days	21/284 (7.4%)	22/273 (8.1%)	43/557 (7.7%)
15 - 21 days	8/284 (2.8%)	14/273 (5.1%)	22/557 (3.9%)
22 - 28 days	60/284 (21.1%)	52/273 (19.0%)	112/557 (20.1%)
29 - 40 days	172/284 (60.6%)	156/273 (57.1%)	328/557 (58.9%)
40+ days	2/284 (0.7%)	4/273 (1.5%)	6/557 (1.1%)
Bottles completed			
n	287	275	562
Mean (SD)	23.7 (8.31)	23.0 (8.98)	23.4 (8.65)
Median (Q1; Q3)	28.0 (26.0; 28.0)	28.0 (21.7; 28.0)	28.0 (25.0; 28.0)
min max	0 28	0 28	0 28
Complete ≥80% of medication	224/287 (78.0%)	205/275 (74.5%)	429/562 (76.3%)
Complete study medication following protocol [1]	189/287 (65.9%)	170/275 (61.8%)	359/562 (63.9%)

Characteristics	FYTF-919 (N = 287)	Placebo (N = 275)	Overall (N = 562)

d. Clinical outcomes

	FYTF-919 (N = 287)	Placebo (N = 275)	Overall (N = 562)
Utility weighted mRS at Day 90			
n	283	273	556
Mean (SD)	0.479 (0.3575)	0.457 (0.3637)	0.468 (0.3604)
Median (Q1; Q3)	0.550 (0.200; 0.880)	0.550 (0.200; 0.740)	0.550 (0.200; 0.810)
min max	-0.19 0.97	-0.19 0.97	-0.19 0.97
Death or disability (mRS 4-6) at Day 28	160/277 (57.8%)	154/264 (58.3%)	314/541 (58.0%)
Death or disability (mRS 4-6) at Day 90	120/283 (42.4%)	115/273 (42.1%)	235/556 (42.3%)
Death at Day 28	22/287 (7.7%)	24/275 (8.7%)	46/562 (8.2%)
Death at Day 90	33/287 (11.5%)	32/275 (11.6%)	65/562 (11.6%)
Disability (mRS 4-5) at Day 28	138/277 (49.8%)	130/264 (49.2%)	268/541 (49.5%)
Disability (mRS 4-5) at Day 90	87/283 (30.7%)	83/273 (30.4%)	170/556 (30.6%)
Stroke associated pneumonia (SAP)	7/266 (2.6%)	7/266 (2.6%)	14/532 (2.6%)
Hospital discharge by Day 28	210/269 (78.1%)	211/259 (81.5%)	421/528 (79.7%)

Table S20. Outcomes in male participants

b. Adherence to study medication

Characteristics	FYTF-919 (N = 528)	Placebo (N = 551)	Overall (N = 1079)
Duration of study treatment (Days)			
n	520	548	1068
Mean (SD)	24.3 (10.30)	25.5 (9.22)	24.9 (9.78)
Median (Q1; Q3)	29.0 (22.5; 29.0)	29.0 (28.0; 29.0)	29.0 (26.5; 29.0)
min max	1 108	1 103	1 108
Duration of study treatment by category			
1 - 7 days	55/520 (10.6%)	43/548 (7.8%)	98/1068 (9.2%)
8 - 14 days	49/520 (9.4%)	34/548 (6.2%)	83/1068 (7.8%)
15 - 21 days	23/520 (4.4%)	28/548 (5.1%)	51/1068 (4.8%)
22 - 28 days	117/520 (22.5%)	117/548 (21.4%)	234/1068 (21.9%)
29 - 40 days	273/520 (52.5%)	319/548 (58.2%)	592/1068 (55.4%)
40+ days	3/520 (0.6%)	7/548 (1.3%)	10/1068 (0.9%)
Bottles completed			
n	528	551	1079
Mean (SD)	22.3 (9.46)	23.7 (8.26)	23.0 (8.89)
Median (Q1; Q3)	28.0 (18.0; 28.0)	28.0 (26.0; 28.0)	28.0 (23.0; 28.0)
min max	0 28	0 28	0 28
Complete ≥80% of medication	384/528 (72.7%)	429/551 (77.9%)	813/1079 (75.3%)
Complete study medication following protocol[1]	302/528 (57.2%)	333/551 (60.4%)	635/1079 (58.9%)

Characteristics	FYTF-919 (N = 528)	Placebo (N = 551)	Overall (N = 1079)

b. Clinical outcomes

	FYTF-919 (N = 528)	Placebo (N = 551)	Overall (N = 1079)
Utility weighted mRS at Day 90			
n	518	545	1063
Mean (SD)	0.517 (0.3472)	0.514 (0.3561)	0.515 (0.3516)
Median (Q1; Q3)	0.550 (0.200; 0.880)	0.550 (0.200; 0.880)	0.550 (0.200; 0.880)
min max	-0.19 0.97	-0.19 0.97	-0.19 0.97
Death or disability (mRS 4-6) at Day 28	273/510 (53.5%)	294/536 (54.9%)	567/1046 (54.2%)
Death or disability (mRS 4-6) at Day 90	186/518 (35.9%)	196/545 (36.0%)	382/1063 (35.9%)
Death at Day 28	51/528 (9.7%)	46/550 (8.4%)	97/1078 (9.0%)
Death at Day 90	65/528 (12.3%)	61/551 (11.1%)	126/1079 (11.7%)
Disability (mRS 4-5) at Day 28	222/510 (43.5%)	248/536 (46.3%)	470/1046 (44.9%)
Disability (mRS 4-5) at Day 90	121/518 (23.4%)	135/545 (24.8%)	256/1063 (24.1%)
Stroke associated pneumonia (SAP)	24/498 (4.8%)	23/513 (4.5%)	47/1011 (4.6%)
Hospital discharge by Day 28	400/482 (83.0%)	415/515 (80.6%)	815/997 (81.7%)

Table S21. Per-protocol dataset of baseline characteristics

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Age (Years)			
n	769	777	1546
Mean (SD)	62.3 (11.95)	61.4 (11.86)	61.8 (11.91)
Median (Q1; Q3)	62.0 (54.0; 71.0)	61.0 (53.0; 70.0)	62.0 (54.0; 71.0)
min max	29 97	18 94	18 97
Sex			
Male	495/769 (64.4%)	519/777 (66.8%)	1014/1546 (65.6%)
Female	274/769 (35.6%)	258/777 (33.2%)	532/1546 (34.4%)
Ethnicity			
Han	744/769 (96.7%)	748/777 (96.3%)	1492/1546 (96.5%)
Non-Han Minorities	25/769 (3.3%)	29/777 (3.7%)	54/1546 (3.5%)
Height (cm)			
n	657	668	1325
Mean (SD)	165.6 (7.94)	166.4 (7.86)	166.0 (7.91)
Median (Q1; Q3)	167.0 (160.0; 172.0)	168.0 (160.0; 172.0)	168.0 (160.0; 172.0)
min max	140 183	140 183	140 183
Weight (Kg)			
n	585	603	1188
Mean (SD)	66.5 (12.63)	67.4 (12.03)	66.9 (12.33)
Median (Q1; Q3)	65.0 (58.0; 75.0)	66.0 (60.0; 75.0)	65.0 (60.0; 75.0)

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
min max	33 120	30 115	30 120
BMI (Kg/m2)			
n	583	602	1185
Mean (SD)	24.0 (3.64)	24.2 (3.39)	24.1 (3.51)
Median (Q1; Q3)	24.0 (21.5; 26.0)	24.2 (22.0; 26.3)	24.1 (21.7; 26.1)
min max	15 46	13 36	13 46
Current smoking			
No	569/769 (74.0%)	560/776 (72.2%)	1129/1545 (73.1%)
Yes	200/769 (26.0%)	216/776 (27.8%)	416/1545 (26.9%)
Current drinking			
No	570/768 (74.2%)	572/776 (73.7%)	1142/1544 (74.0%)
Yes	198/768 (25.8%)	204/776 (26.3%)	402/1544 (26.0%)
SBP on arrival			
n	766	775	1541
Mean (SD)	171.6 (28.90)	171.2 (28.82)	171.4 (28.85)
Median (Q1; Q3)	170.0 (150.0; 190.0)	171.0 (150.0; 190.0)	171.0 (150.0; 190.0)
min max	82 265	91 261	82 265
DBP on arrival			
n	766	775	1541
Mean (SD)	98.1 (18.72)	98.5 (19.68)	98.3 (19.20)
Median (Q1; Q3)	98.0 (86.0; 110.0)	98.0 (85.0; 110.0)	98.0 (85.0; 110.0)

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
min max	42 167	11 197	11 197
Heart rate on arrival			
n	768	776	1544
Mean (SD)	79.5 (15.10)	80.4 (14.96)	79.9 (15.03)
Median (Q1; Q3)	80.0 (69.0; 88.0)	80.0 (70.0; 88.5)	80.0 (70.0; 88.0)
min max	46 208	20 140	20 208
Respiratory rate on arrival			
n	755	757	1512
Mean (SD)	19.2 (3.85)	19.3 (3.65)	19.3 (3.75)
Median (Q1; Q3)	19.0 (18.0; 20.0)	19.0 (18.0; 20.0)	19.0 (18.0; 20.0)
min max	10 98	10 76	10 98
Body temperature on arrival			
n	769	776	1545
Mean (SD)	36.59 (0.355)	36.62 (0.406)	36.61 (0.381)
Median (Q1; Q3)	36.50 (36.40; 36.80)	36.60 (36.50; 36.80)	36.60 (36.40; 36.80)
min max	35.7 39.1	35.0 39.8	35.0 39.8
first GCS on arrival			
n	741	742	1483
Mean (SD)	11.6 (2.81)	11.7 (2.88)	11.6 (2.85)
Median (Q1; Q3)	12.0 (10.0; 14.0)	12.0 (10.0; 14.0)	12.0 (10.0; 14.0)
min max	3 15	3 15	3 15

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
first NIHSS on arrival			
n	765	769	1534
Mean (SD)	16.2 (7.98)	16.2 (8.05)	16.2 (8.01)
Median (Q1; Q3)	15.0 (10.0; 21.0)	15.0 (10.0; 20.0)	15.0 (10.0; 20.0)
min max	0 42	1 42	0 42
NIHSS category			
NIHSS >=15	415/765 (54.2%)	416/769 (54.1%)	831/1534 (54.2%)
NIHSS < 15	350/765 (45.8%)	353/769 (45.9%)	703/1534 (45.8%)
Time from onset to arrival (hour)			
n	769	777	1546
Mean (SD)	5.5 (6.64)	5.1 (6.08)	5.3 (6.36)
Median (Q1; Q3)	3.1 (2.0; 5.7)	3.0 (1.9; 5.2)	3.0 (1.9; 5.4)
min max	0 47	0 46	0 47
Time from onset to randomisation (hour)			
n	769	777	1546
Mean (SD)	18.0 (12.49)	17.6 (11.79)	17.8 (12.14)
Median (Q1; Q3)	15.1 (7.3; 25.9)	15.4 (7.4; 25.1)	15.2 (7.3; 25.7)
min max	2 58	1 61	1 61
Time from onset to first medicine given (hour)			
n	769	777	1546
Mean (SD)	22.7 (14.11)	22.1 (13.32)	22.4 (13.72)
Median (Q1; Q3)	20.0 (11.1; 31.0)	19.8 (11.5; 29.1)	20.0 (11.3; 30.3)

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
min max	2 109	2 84	2 109
First method of study medication			
Oral admission（awake，33ml/time，tid）	378/767 (49.3%)	381/777 (49.0%)	759/1544 (49.2%)
Nasogastric tube（coma，25ml/time，q6h）	389/767 (50.7%)	396/777 (51.0%)	785/1544 (50.8%)
Previous hypertension	508/767 (66.2%)	535/774 (69.1%)	1043/1541 (67.7%)
Antihypertensive medication	479/508 (94.3%)	505/535 (94.4%)	984/1043 (94.3%)
ACEI ARB	36/479 (7.5%)	49/505 (9.7%)	85/984 (8.6%)
Beta blocker	11/479 (2.3%)	12/505 (2.4%)	23/984 (2.3%)
Ca antagonist	77/479 (16.1%)	91/505 (18.0%)	168/984 (17.1%)
Diuretics	2/479 (0.4%)	5/505 (1.0%)	7/984 (0.7%)
Other antihypertensives	366/479 (76.4%)	369/505 (73.1%)	735/984 (74.7%)
Reserpine Co	5/366 (1.4%)	4/369 (1.1%)	9/735 (1.2%)
Unknown	361/366 (98.6%)	365/369 (98.9%)	726/735 (98.8%)
Previous diabetes	65/769 (8.5%)	70/776 (9.0%)	135/1545 (8.7%)
Antidiabetic medication	24/65 (36.9%)	34/70 (48.6%)	58/135 (43.0%)

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Insulin	1/24 (4.2%)	0/34 (0.0%)	1/58 (1.7%)
Biguanide	3/24 (12.5%)	2/34 (5.9%)	5/58 (8.6%)
Sulfonylurea	1/24 (4.2%)	0/34 (0.0%)	1/58 (1.7%)
Glycosidase inhibitor	2/24 (8.3%)	0/34 (0.0%)	2/58 (3.4%)
Other	20/24 (83.3%)	32/34 (94.1%)	52/58 (89.7%)
Euphridine	1/20 (5.0%)	0/32 (0.0%)	1/52 (1.9%)
Repaglinide	1/20 (5.0%)	0/32 (0.0%)	1/52 (1.9%)
Unknown	18/20 (90.0%)	32/32 (100.0%)	50/52 (96.2%)
Previous hyperlipidaemia	10/769 (1.3%)	9/777 (1.2%)	19/1546 (1.2%)
Lipid lowering agent	8/10 (80.0%)	7/9 (77.8%)	15/19 (78.9%)
Statin	5/8 (62.5%)	3/7 (42.9%)	8/15 (53.3%)
Cholesterol absorption inhibitor	0/8 (0.0%)	0/7 (0.0%)	0/15 (0.0%)
PCSK9 inhibitor	0/8 (0.0%)	0/7 (0.0%)	0/15 (0.0%)
Other (All unknown)	3/8 (37.5%)	4/7 (57.1%)	7/15 (46.7%)

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Previous coronary heart disease	39/769 (5.1%)	27/777 (3.5%)	66/1546 (4.3%)
Previous atrial fibrillation	1/769 (0.1%)	5/777 (0.6%)	6/1546 (0.4%)
Any anticoagulation treatment	1/769 (0.1%)	3/777 (0.4%)	4/1546 (0.3%)
Any antiplatelet treatment	34/769 (4.4%)	26/777 (3.3%)	60/1546 (3.9%)
Aspirin	30/34 (88.2%)	23/26 (88.5%)	53/60 (88.3%)
Clopidogrel	8/34 (23.5%)	6/26 (23.1%)	14/60 (23.3%)
Other	1/34 (2.9%)	2/26 (7.7%)	3/60 (5.0%)
Total TCM score (TCM 1-5)			
n	738	740	1478
Mean (SD)	1.1 (1.25)	1.1 (1.26)	1.1 (1.25)
Median (Q1; Q3)	1.0 (0.0; 2.0)	1.0 (0.0; 2.0)	1.0 (0.0; 2.0)
min max	0 5	0 5	0 5
Anxiety	91/737 (12.3%)	83/740 (11.2%)	174/1477 (11.8%)
Red face/T>37.5	148/737 (20.1%)	151/739 (20.4%)	299/1476 (20.3%)
Dry mouth/Bad breath	181/732 (24.7%)	184/735 (25.0%)	365/1467 (24.9%)

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Yellow tongue coating	161/718 (22.4%)	167/725 (23.0%)	328/1443 (22.7%)
Red tongue coating	250/718 (34.8%)	246/724 (34.0%)	496/1442 (34.4%)
No Stool in the last 48h	227/738 (30.8%)	251/737 (34.1%)	478/1475 (32.4%)

Table S22. Study medication in the per protocol population

Characteristics	FYTF-919 (N=769)	Placebo (N=777)	Overall (N=1546)
Duration of study treatment (Days)			
n	768	777	1545
Mean (SD)	25.3 (9.89)	25.8 (8.77)	25.5 (9.34)
Median (Q1; Q3)	768	777	1545
min max	1 108	1 103	1 108
Duration of study treatment by category			
1 - 7 days	62/768 (8.1%)	53/777 (6.8%)	116/1545 (7.4%)
8 - 14 days	68/768 (8.9%)	51/777 (6.6%)	119/1545 (7.7%)
15 - 21 days	28/768 (3.6%)	40/777 (5.1%)	68/1545 (4.4%)
22 - 28 days	168/768 (21.9%)	161/777 (20.7%)	329/1545 (21.3%)
29 - 40 days	437/768 (56.9%)	461/777 (59.3%)	898/1545 (58.1%)
40+ days	5/768 (0.7%)	11/777 (1.4%)	16/1545 (1.0%)
Bottles completed			
n	769	777	1546
Mean (SD)	23.5 (8.37)	24.1 (7.75)	23.8 (8.07)
Median (Q1; Q3)	28.0 (25.0; 28.0)	28.0 (26.3; 28.0)	28.0 (26.0; 28.0)
min max	1 28	0 28	0 28
Complete ≥80% of medication	592/769 (77.0%)	613/777 (78.9%)	1205/1546 (77.9%)
Complete study medication following protocol [1]	476/769 (61.9%)	487/777 (62.7%)	963/1546 (62.3%)

Table S23. Clinical assessment of outcomes over time in the per protocol population

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
NIHSS			
Baseline			
n	765	769	1534
Mean (SD)	16.2 (7.98)	16.2 (8.05)	16.2 (8.01)
Median (Q1; Q3)	15.0 (10.0; 21.0)	15.0 (10.0; 20.0)	15.0 (10.0; 20.0)
min max	0 42	1 42	0 42
Follow up 1 - 24h(±3h)			
n	736	748	1484
Mean (SD)	16.1 (8.26)	16.3 (8.52)	16.2 (8.39)
Median (Q1; Q3)	15.0 (10.0; 21.0)	15.0 (10.0; 21.0)	15.0 (10.0; 21.0)
min max	0 42	0 41	0 42
Follow up 2 - D7±D1			
n	726	732	1458
Mean (SD)	13.3 (8.26)	13.8 (8.70)	13.5 (8.49)
Median (Q1; Q3)	12.0 (8.0; 18.0)	12.0 (7.0; 18.5)	12.0 (7.0; 18.0)
min max	0 40	0 40	0 40
Follow up 3 - D14±D2			
n	648	666	1314
Mean (SD)	10.9 (7.64)	11.6 (8.12)	11.3 (7.89)
Median (Q1; Q3)	10.0 (5.0; 15.0)	10.0 (6.0; 15.0)	10.0 (6.0; 15.0)

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
min max	0 39	0 41	0 41
Follow up 4 - D28±D3			
n	515	526	1041
Mean (SD)	8.3 (7.12)	9.0 (7.58)	8.7 (7.36)
Median (Q1; Q3)	7.0 (3.0; 12.0)	7.0 (3.0; 12.0)	7.0 (3.0; 12.0)
min max	0 37	0 42	0 42
GCS			
Baseline			
n	741	742	1483
Mean (SD)	11.6 (2.81)	11.7 (2.88)	11.6 (2.85)
Median (Q1; Q3)	12.0 (10.0; 14.0)	12.0 (10.0; 14.0)	12.0 (10.0; 14.0)
min max	3 15	3 15	3 15
Follow up 1 - 24h(±3h)			
n	718	713	1431
Mean (SD)	11.6 (2.94)	11.7 (2.97)	11.7 (2.95)
Median (Q1; Q3)	12.0 (10.0; 14.0)	13.0 (10.0; 14.0)	12.0 (10.0; 14.0)
min max	2 15	3 15	2 15
Follow up 2 - D7±D1			
n	696	686	1382
Mean (SD)	12.8 (2.73)	12.7 (2.81)	12.7 (2.77)
Median (Q1; Q3)	14.0 (11.0; 15.0)	14.0 (11.0; 15.0)	14.0 (11.0; 15.0)

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
min max	3 15	3 15	3 15
Follow up 3 - D14±D2			
n	644	649	1293
Mean (SD)	13.5 (2.27)	13.4 (2.59)	13.4 (2.44)
Median (Q1; Q3)	15.0 (12.0; 15.0)	15.0 (13.0; 15.0)	15.0 (12.0; 15.0)
min max	3 15	2 15	2 15
Follow up 4 - D28±D3			
n	568	580	1148
Mean (SD)	14.1 (1.80)	14.0 (2.07)	14.1 (1.94)
Median (Q1; Q3)	15.0 (14.0; 15.0)	15.0 (14.0; 15.0)	15.0 (14.0; 15.0)
min max	5 15	3 15	3 15
mRS			
Baseline (Before stroke onset)			
0: No symptoms	696/768 (90.6%)	705/777 (90.7%)	1401/1545 (90.7%)
1: No significant disability	46/768 (6.0%)	40/777 (5.1%)	86/1545 (5.6%)
2: Slight disability	26/768 (3.4%)	32/777 (4.1%)	58/1545 (3.8%)
3: Moderate disability	0/768 (0.0%)	0/777 (0.0%)	0/1545 (0.0%)
4: Moderately severe disability	0/768 (0.0%)	0/777 (0.0%)	0/1545 (0.0%)
5: Severe disability	0/768 (0.0%)	0/777 (0.0%)	0/1545 (0.0%)
6: Death	0/768 (0.0%)	0/777 (0.0%)	0/1545 (0.0%)
Follow up 4 - D28±D3			

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
0: No symptoms	28/744 (3.8%)	33/751 (4.4%)	61/1495 (4.1%)
1: No significant disability	119/744 (16.0%)	102/751 (13.6%)	221/1495 (14.8%)
2: Slight disability	90/744 (12.1%)	87/751 (11.6%)	177/1495 (11.8%)
3: Moderate disability	99/744 (13.3%)	108/751 (14.4%)	207/1495 (13.8%)
4: Moderately severe disability	281/744 (37.8%)	267/751 (35.6%)	548/1495 (36.7%)
5: Severe disability	62/744 (8.3%)	92/751 (12.3%)	154/1495 (10.3%)
6: Death	65/744 (8.7%)	62/751 (8.3%)	127/1495 (8.5%)
Follow up 5 - D90±D7			
0: No symptoms	61/757 (8.1%)	60/770 (7.8%)	121/1527 (7.9%)
1: No significant disability	147/757 (19.4%)	149/770 (19.4%)	296/1527 (19.4%)
2: Slight disability	113/757 (14.9%)	116/770 (15.1%)	229/1527 (15.0%)
3: Moderate disability	148/757 (19.6%)	151/770 (19.6%)	299/1527 (19.6%)
4: Moderately severe disability	171/757 (22.6%)	163/770 (21.2%)	334/1527 (21.9%)
5: Severe disability	29/757 (3.8%)	48/770 (6.2%)	77/1527 (5.0%)
6: Death	88/757 (11.6%)	83/770 (10.8%)	171/1527 (11.2%)
Barthel Index			
Follow up 4 - D28±D3			
n	677	689	1366
Mean (SD)	56.0 (32.61)	53.9 (33.18)	54.9 (32.91)
Median (Q1; Q3)	55.0 (25.0; 90.0)	50.0 (25.0; 85.0)	55.0 (25.0; 90.0)
min max	0 100	0 100	0 100
Follow up 5 - D90±D7			

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
n	670	690	1360
Mean (SD)	71.0 (29.22)	69.5 (30.21)	70.2 (29.73)
Median (Q1; Q3)	80.0 (50.0; 100.0)	80.0 (50.0; 100.0)	80.0 (50.0; 100.0)
min max	0 100	0 100	0 100
EQ5D5L VAS			
Follow up 4 - D28±D3			
n	667	681	1348
Mean (SD)	63.4 (24.23)	62.6 (25.08)	63.0 (24.66)
Median (Q1; Q3)	70.0 (50.0; 80.0)	65.0 (50.0; 80.0)	65.0 (50.0; 80.0)
min max	0 100	0 100	0 100
Follow up 5 - D90±D7			
n	670	689	1359
Mean (SD)	72.0 (22.16)	71.4 (22.35)	71.7 (22.25)
Median (Q1; Q3)	77.0 (60.0; 90.0)	80.0 (60.0; 90.0)	80.0 (60.0; 90.0)
min max	0 100	0 100	0 100
EQ5D5L Utility score in survivors			
Follow up 4 - D28±D3			
n	668	680	1348
Mean (SD)	0.419 (0.4142)	0.409 (0.4104)	0.414 (0.4122)
Median (Q1; Q3)	0.374 (0.090; 0.827)	0.363 (0.062; 0.800)	0.363 (0.062; 0.827)
min max	-0.39 1.00	-0.39 1.00	-0.39 1.00

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Follow up 5 - D90±D7			
n	669	687	1356
Mean (SD)	0.580 (0.3957)	0.582 (0.3851)	0.581 (0.3902)
Median (Q1; Q3)	0.734 (0.212; 0.942)	0.720 (0.201; 0.934)	0.728 (0.208; 0.942)
min max	-0.39 1.00	-0.39 1.00	-0.39 1.00
EQ5D5L Utility score imputing Death as zero			
Follow up 4 - D28±D3			
n	733	742	1475
Mean (SD)	0.382 (0.4129)	0.375 (0.4089)	0.378 (0.4108)
Median (Q1; Q3)	0.220 (0.024; 0.783)	0.218 (0.000; 0.783)	0.220 (0.013; 0.783)
min max	-0.39 1.00	-0.39 1.00	-0.39 1.00
Follow up 5 - D90±D7			
n	757	770	1527
Mean (SD)	0.513 (0.4159)	0.519 (0.4060)	0.516 (0.4108)
Median (Q1; Q3)	0.620 (0.101; 0.893)	0.596 (0.120; 0.898)	0.620 (0.112; 0.898)
min max	-0.39 1.00	-0.39 1.00	-0.39 1.00

Table S24: Descriptives of outcomes in the per protocol population at 28 and 90 days

	FYTF-919 (N=815)	**Placebo (N=826)**	**Overall (N=1641)**
Utility weighted mRS at Day 90			
n	738	748	1526
Mean (SD)	0.505 (0.3503)	0.496 (0.3608)	0.500 (0.3555)
Median (Q1; Q3)	0.550 (0.200; 0.880)	0.550 (0.200; 0.880)	0.550 (0.200; 0.880)
min max	-0.19 0.97	-0.19 0.97	-0.19 0.97
Death or disability (mRS 4-6) at Day 28	408/744 (54.8%)	421/751 (56.1%)	829/1495 (55.5%)
Death or disability (mRS 4-6) at Day 90	288/757 (38.0%)	294/770 (38.2%)	582/1527 (38.1%)
Death at Day 28	65/769 (8.5%)	62/777 (8.0%)	127/1546 (8.2%)
Death at Day 90	88/769 (11.4%)	83/777 (10.7%)	171/1546 (11.1%)
Disability (mRS 4-5) at Day 28	343/744 (46.1%)	359/751 (47.8%)	702/1495 (47.0%)
Disability (mRS 4-5) at Day 90	200/757 (26.4%)	211/770 (27.4%)	411/1527 (26.9%)
Stroke associated pneumonia (SAP)	31/725 (4.3%)	28/737 (3.8%)	59/1462 (4.0%)
Hospital discharge by Day 28	581/712 (81.6%)	597/733 (81.4%)	1178/1445 (81.5%)

Table S25. Modelling results of the outcomes in the per protocol population 1.

		Primary model (1)			Adjusted model (2)	
Outcome	**N***	**OR/MD(95%CI)****	**p value**	**N***	**OR/MD(95%CI)****	**p value**
Primary Outcome						
uwMRS Day 90	1486	0.008 (-0.023, 0.040)	0.60	1485	0.015 (-0.015, 0.046)	0.32
uwMRS Day 90 - sensitivity 1	1486	0.005 (-0.029, 0.038)	0.79			
uwMRS Day 90 - sensitivity 2	1325	0.003 (-0.030, 0.036)	0.85			
uwMRS Day 90 - sensitivity 3	1486	0.005 (-0.029, 0.038)	0.79			
Secondary Outcomes						
Ordinal mRS Day 28**	1460	0.87 (0.73, 1.05)	0.15	1459	0.84 (0.70, 1.02)	0.07
Ordinal mRS Day 90**	1486	1.00 (0.84, 1.20)	0.96	1485	0.96 (0.80, 1.15)	0.68
Death or disability - mRS [4-6] Day 28**	1460	0.92 (0.72, 1.17)	0.50	1459	0.89 (0.70, 1.14)	0.36
Death or disability - mRS [4-6] Day 90**	1486	0.99 (0.78, 1.25)	0.93	1485	0.93 (0.73, 1.18)	0.54
Death Day 28**	1503	1.02 (0.69, 1.50)	0.92	1502	0.94 (0.63, 1.41)	0.77
Death Day 90**	1503	1.05 (0.75, 1.47)	0.78	1502	0.97 (0.68, 1.39)	0.87
Disability - mRS [4-5] Day 28**	1460	0.91 (0.73, 1.15)	0.44	1459	0.91 (0.72, 1.15)	0.43
Disability - mRS [4-5] Day 90**	1486	0.96 (0.75, 1.22)	0.72	1485	0.94 (0.73, 1.20)	0.61
NIHSS Day 1	1452	-0.20 (-0.78, 0.39)	0.51	1451	-0.22 (-0.81, 0.36)	0.45
NIHSS Day 7	1425	-0.55 (-1.24, 0.14)	0.12	1424	-0.60 (-1.29, 0.08)	0.09
Barthel Index Day 28	1338	1.90 (-1.08, 4.88)	0.21	1337	2.26 (-0.71, 5.23)	0.14
Barthel Index Day 90	1325	0.67 (-2.18, 3.51)	0.65	1324	1.21 (-1.58, 4.00)	0.39

Outcome	Primary model (1) N*	Primary model (1) OR/MD(95%CI)**	Primary model (1) p value	Adjusted model (2) N*	Adjusted model (2) OR/MD(95%CI)**	Adjusted model (2) p value
EQ5D5L VAS in survivors Day 28	1252	0.41 (-1.90, 2.72)	0.73	1251	0.56 (-1.72, 2.87)	0.63
EQ5D5L VAS in survivors Day 90	1294	-0.43 (-2.54, 1.67)	0.69	1293	-0.23 (-2.33, 1.87)	0.83
EQ5D5L Utility score in survivors Day 28	1254	0.00 (-0.03, 0.04)	0.85	1253	0.01 (-0.03, 0.04)	0.75
EQ5D5L Utility score in survivors Day 90	1294	-0.01 (-0.05, 0.02)	0.48	1293	-0.01 (-0.04, 0.03)	0.69
EQ5D5L VAS Day 28 (impute death = 0)	1441	0.59 (-2.10, 3.27)	0.667	1440	0.97 (-1.68, 3.61)	0.47
EQ5D5L VAS Day 90 (impute death = 0)	1485	-0.30 (-3.13, 2.53)	0.84	1484	0.21 (-2.53, 2.96)	0.88
EQ5D5L Utility score Day 28 (impute death = 0)	1445	0.01 (-0.03, 0.05)	0.57	1444	0.01 (-0.02, 0.05)	0.44
EQ5D5L Utility score Day 90 (impute death = 0)	1486	-0.01 (-0.04, 0.03)	0.76	1485	0.00 (-0.03, 0.04)	0.93
Any SAP**	1420	1.11 (0.63, 1.95)	0.72	1420	1.09 (0.62, 1.93)	0.76
Discharge alive within 28 days	1411	0.95 (0.69, 1.30)	0.74	1410	0.97 (0.71, 1.34)	0.87

Table S11. Modelling results of the outcomes in the per protocol population 2.

	Primary model						Adjusted model					
	Intervention			Control			Intervention			Control		
Outcome	**N**	**Mean**	**%**	**N**	**Mean**	**%**	**N**	**Mean**	**%**	**N**	**Mean**	**%**
uwMRS Day 90 - adjusted	738	0.45		748	0.44		737	0.43		748	0.42	
uwMRS Day 90 - sensitivity 1	738	0.47		748	0.46		737	0.52		748	0.51	
uwMRS Day 90 - sensitivity 2	655	0.56		670	0.56		654	0.58		670	0.57	
uwMRS Day 90 - sensitivity 3	738	0.47		748	0.46		737	0.52		748	0.51	
Ordinal mRS Day 28												
Ordinal mRS Day 90												
Death or disability - mRS [4-6] Day 28	726	43.5		734	57.3		725	52.4		734	55.2	
Death or disability - mRS [4-6] Day 90	738	43.5		748	43.7		737	46.2		748	48.1	
Death Day 28	749	11.2		753	11.0		748	12.0		753	12.6	
Death Day 90	749	16.3		754	15.7		748	17.7		754	18.2	
Disability - mRS [4-5] Day 28	726	20.6		734	22.1		725	46.2		734	47.8	
Disability - mRS [4-5] Day 90	738	26.6		748	22.0		737	26.6		748	27.1	
NIHSS Day 1	720	15.72		732	15.92		719	15.97		732	16.19	
NIHSS Day 7	710	12.83		715	13.38		709	12.99		715	13.60	
Barthel Index Day 28	664	54.49		674	52.59		663	54.92		674	52.65	
Barthel Index Day 90	655	69.40		670	68.74		654	67.58		670	66.36	

	Primary model						Adjusted model					
	Intervention			Control			Intervention			Control		
Outcome	**N**	**Mean**	**%**	**N**	**Mean**	**%**	**N**	**Mean**	**%**	**N**	**Mean**	**%**
EQ5D5L VAS in survivors Day 28	623	61.48		629	61.06		622	63.41		629	62.85	
EQ5D5L VAS in survivors Day 90	642	70.35		652	70.78		641	70.71		652	70.94	
EQ5D5L Utility score in survivors Day 28	624	0.44		630	0.43		623	0.45		630	0.45	
EQ5D5L Utility score in survivors Day 90	642	0.58		652	0.60		641	0.56		652	0.57	
EQ5D5L VAS Day 28 (impute death = 0)	716	51.91		725	51.33		715	51.56		725	50.59	
EQ5D5L VAS Day 90 (impute death = 0)	738	56.15		747	56.45		737	54.07		747	53.86	
EQ5D5L Utility score Day 28 (impute death = 0)	719	0.37		726	0.36		718	0.37		726	0.35	
EQ5D5L Utility score Day 90 (impute death = 0)	738	0.46		748	0.47		737	0.44		748	0.44	
Any SAP	706		0.005	714		0.005	706		0.004	714		0.003
Discharge alive within 28 days	697		96.1	714		96.3	696		96.0	714		96.1

Table S27. Analysis for the outcomes at 180 days:

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Utility weighted mRS			
n	814	826	1640
Mean (SD)	0.55 (0.36)	0.55 (0.36)	0.55 (0.36)
Median (Q1; Q3)	0.55 (0.20; 0.88)	0.55 (0.20; 0.88)	0.55 (0.20; 0.88)
min max	-0.19 0.97	-0.19 0.97	-0.19 0.97
Death or disability (mRS 4-6)	262/814 (32.2%)	262/826 (31.7%)	524/1640 (32.0%)
Death	113/815 (13.9%)	111/826 (13.4%)	224/1641 (13.7%)
Disability (mRS 4-5)	149/814 (18.3%)	151/826 (18.3%)	300/1640 (18.3%)

mRS denotes modified Rankin scale

Table S28. Causes of death until 90 days

Overcome	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Death by Day 90			
No	717/815 (88.0)	733/826 (88.7)	1450/1641 (88.4)
Yes	98/815 (12.0)	93/826 (11.3)	191/1641 (11.6)
Cause of death			
CNS damage from index stroke*	51/96 (53.1)	40/92 (43.5)	91/188 (48.4)
Lung infection	11/96 (11.5)	14/92 (15.2)	25/188 (13.3)
Cardiovascular disease	3/96 (3.1)	2/92 (2.2)	5/188 (2.7)
Stroke recurrence	1/96 (1.0)	4/92 (4.3)	5/188 (2.7)
Other	30/96 (31.3)	32/92 (34.8)	62/188 (33.0)
Respiratory failure	5/30 (16.7)	5/32 (15.6)	10/62 (16.1)
Respiratory and circulatory failure	1/30 (3.3)	2/32 (6.3)	3/62 (4.8)
Gastrointestinal bleeding	1/30 (3.3)	1/32 (3.1)	2/62 (3.2)
Heart failure	2/30 (6.7)	0/32 (0.0)	2/62 (3.2)
Multiple organ failure	1/30 (3.3)	1/32 (3.1)	2/62 (3.2)
Cachectic state	1/30 (3.3)	0/32 (0.0)	1/62 (1.6)
Circulatory / respiratory failure	0/30 (0.0)	1/32 (3.1)	1/62 (1.6)
Epilepsy	1/30 (3.3)	0/32 (0.0)	1/62 (1.6)
Pulmonary embolism	0/30 (0.0)	1/32 (3.1)	1/62 (1.6)
Septicaemia	1/30 (3.3)	0/32 (0.0)	1/62 (1.6)
Sudden death	1/30 (3.3)	0/32 (0.0)	1/62 (1.6)
Unknown	16/30 (53.3)	21/32 (65.6)	37/62 (59.7)

Data are n (%)

*CNS denotes central nervous system

Table S29. Reported stroke-related complications by visit until 90 days

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Respiratory infection			
Baseline	275/815 (33.7)	309/826 (37.4)	584/1641 (35.6)
Follow up 1 - 24h(±3h)	324/815 (39.8)	364/825 (44.1)	688/1640 (42.0)
Follow up 2 - D7±D1	361/802 (45.0)	397/812 (48.9)	758/1614 (47.0)
Follow up 3 - D14±D2	245/752 (32.6)	265/778 (34.1)	510/1530 (33.3)
Follow up 4 - D28±D3	128/718 (17.8)	145/732 (19.8)	273/1450 (18.8)
Urinary tract infection			
Baseline	6/815 (0.7)	4/826 (0.5)	10/1641 (0.6)
Follow up 1 - 24h(±3h)	10/815 (1.2)	2/825 (0.2)	12/1640 (0.7)
Follow up 2 - D7±D1	16/802 (2.0)	7/812 (0.9)	23/1614 (1.4)
Follow up 3 - D14±D2	21/752 (2.8)	10/778 (1.3)	31/1530 (2.0)
Follow up 4 - D28±D3	15/718 (2.1)	12/732 (1.6)	27/1450 (1.9)
Intestinal infection			
Baseline	1/815 (0.1)	0/826 (0.0)	1/1641 (0.1)
Follow up 1 - 24h(±3h)	0/815 (0.0)	0/825 (0.0)	0/1640 (0.0)
Follow up 2 - D7±D1	0/802 (0.0)	0/812 (0.0)	0/1614 (0.0)
Follow up 3 - D14±D2	0/752 (0.0)	0/778 (0.0)	0/1530 (0.0)
Follow up 4 - D28±D3	0/718 (0.0)	1/732 (0.1)	1/1450 (0.1)
Other infection			
Baseline	2/815 (0.2)	1/826 (0.1)	3/1641 (0.2)
Follow up 1 - 24h(±3h)	7/815 (0.9)	8/825 (1.0)	15/1640 (0.9)
Follow up 2 - D7±D1	16/802 (2.0)	18/812 (2.2)	34/1614 (2.1)
Follow up 3 - D14±D2	18/752 (2.4)	18/778 (2.3)	36/1530 (2.4)
Follow up 4 - D28±D3	11/718 (1.5)	13/732 (1.8)	24/1450 (1.7)

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Acute renal injury			
Baseline	0/815 (0.0)	1/826 (0.1)	1/1641 (0.1)
Follow up 1 - 24h(±3h)	1/815 (0.1)	1/825 (0.1)	2/1640 (0.1)
Follow up 2 - D7±D1	2/802 (0.2)	2/812 (0.2)	4/1614 (0.2)
Follow up 3 - D14±D2	2/752 (0.3)	1/778 (0.1)	3/1530 (0.2)
Follow up 4 - D28±D3	1/718 (0.1)	0/732 (0.0)	1/1450 (0.1)
Gastrointestinal haemorrhage			
Baseline	19/815 (2.3)	23/826 (2.8)	42/1641 (2.6)
Follow up 1 - 24h(±3h)	25/815 (3.1)	27/825 (3.3)	52/1640 (3.2)
Follow up 2 - D7±D1	24/802 (3.0)	26/812 (3.2)	50/1614 (3.1)
Follow up 3 - D14±D2	22/752 (2.9)	17/778 (2.2)	39/1530 (2.5)
Follow up 4 - D28±D3	13/718 (1.8)	18/732 (2.5)	31/1450 (2.1)
Hyperosmolar coma			
Baseline	0/815 (0.0)	0/826 (0.0)	0/1641 (0.0)
Follow up 1 - 24h(±3h)	0/815 (0.0)	0/825 (0.0)	0/1640 (0.0)
Follow up 2 - D7±D1	0/802 (0.0)	0/812 (0.0)	0/1614 (0.0)
Follow up 3 - D14±D2	0/752 (0.0)	0/778 (0.0)	0/1530 (0.0)
Follow up 4 - D28±D3	0/718 (0.0)	0/732 (0.0)	0/1450 (0.0)
Pulmonary embolism			
Baseline	0/815 (0.0)	0/826 (0.0)	0/1641 (0.0)
Follow up 1 - 24h(±3h)	0/815 (0.0)	0/825 (0.0)	0/1640 (0.0)
Follow up 2 - D7±D1	0/802 (0.0)	0/812 (0.0)	0/1614 (0.0)
Follow up 3 - D14±D2	0/752 (0.0)	1/778 (0.1)	1/1530 (0.1)
Follow up 4 - D28±D3	1/718 (0.1)	1/732 (0.1)	2/1450 (0.1)
Raised intracranial pressure or herniation			

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Baseline	45/815 (5.5)	53/826 (6.4)	98/1641 (6.0)
Follow up 1 - 24h(±3h)	31/815 (3.8)	51/825 (6.2)	82/1640 (5.0)
Follow up 2 - D7±D1	23/802 (2.9)	29/812 (3.6)	52/1614 (3.2)
Follow up 3 - D14±D2	8/752 (1.1)	16/778 (2.1)	24/1530 (1.6)
Follow up 4 - D28±D3	3/718 (0.4)	7/732 (1.0)	10/1450 (0.7)
Hydrocephalus			
Baseline	11/815 (1.3)	17/826 (2.1)	28/1641 (1.7)
Follow up 1 - 24h(±3h)	5/815 (0.6)	21/825 (2.5)	26/1640 (1.6)
Follow up 2 - D7±D1	7/802 (0.9)	15/812 (1.8)	22/1614 (1.4)
Follow up 3 - D14±D2	2/752 (0.3)	11/778 (1.4)	13/1530 (0.8)
Follow up 4 - D28±D3	1/718 (0.1)	6/732 (0.8)	7/1450 (0.5)
Intracranial re-haemorrhage			
Baseline	5/815 (0.6)	8/826 (1.0)	13/1641 (0.8)
Follow up 1 - 24h(±3h)	10/815 (1.2)	11/825 (1.3)	21/1640 (1.3)
Follow up 2 - D7±D1	11/802 (1.4)	13/812 (1.6)	24/1614 (1.5)
Follow up 3 - D14±D2	3/752 (0.4)	5/778 (0.6)	8/1530 (0.5)
Follow up 4 - D28±D3	0/718 (0.0)	6/732 (0.8)	6/1450 (0.4)
Hyperthermia			
Baseline	7/815 (0.9)	6/826 (0.7)	13/1641 (0.8)
Follow up 1 - 24h(±3h)	15/815 (1.8)	11/825 (1.3)	26/1640 (1.6)
Follow up 2 - D7±D1	13/802 (1.6)	10/812 (1.2)	23/1614 (1.4)
Follow up 3 - D14±D2	2/752 (0.3)	4/778 (0.5)	6/1530 (0.4)
Follow up 4 - D28±D3	0/718 (0.0)	0/732 (0.0)	0/1450 (0.0)
Other			
Baseline	93/815 (11.4)	102/826 (12.3)	195/1641 (11.9)

Characteristics	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Follow up 1 - 24h(±3h)	92/815 (11.3)	111/825 (13.5)	203/1640 (12.4)
Follow up 2 - D7±D1	153/802 (19.1)	164/812 (20.2)	317/1614 (19.6)
Follow up 3 - D14±D2	120/752 (16.0)	131/778 (16.8)	251/1530 (16.4)
Follow up 4 - D28±D3	74/718 (10.3)	72/732 (9.8)	146/1450 (10.1)
Any adverse event reported			
Respiratory infection	447/815 (54.8)	483/826 (58.5)	930/1641 (56.7)
Urinary tract infection	39/815 (4.8)	24/826 (2.9)	63/1641 (3.8)
Intestinal infection	1/815 (0.1)	1/826 (0.1)	2/1641 (0.1)
Other infection	33/815 (4.0)	30/826 (3.6)	63/1641 (3.8)
Acute renal injury	3/815 (0.4)	3/826 (0.4)	6/1641 (0.4)
Gastrointestinal haemorrhage	50/815 (6.1)	51/826 (6.2)	101/1641 (6.2)
Hyperosmolar coma	0/815 (0.0)	0/826 (0.0)	0/1641 (0.0)
Pulmonary embolism	1/815 (0.1)	2/826 (0.2)	3/1641 (0.2)
Raised intracranial pressure or herniation	54/815 (6.6)	69/826 (8.4)	123/1641 (7.5)
Hydrocephalus	17/815 (2.1)	32/826 (3.9)	49/1641 (3.0)
Intracranial re-haemorrhage	21/815 (2.6)	29/826 (3.5)	50/1641 (3.0)
Hyperthermia	28/815 (3.4)	25/826 (3.0)	53/1641 (3.2)
Other	253/815 (31.0)	277/826 (33.5)	530/1641 (32.3)

Data are n (%)

Table S30. Adverse events by description until 90 days

Classification	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)	p value
Adverse Event	1761[#] 650/815 (79.8)	1751[#] 665/826 (80.5)	3512[#] 1315/1641 (80.1)	0.70
Relation to treatment				
Definitely related	10/1748 (0.6)	6/1740 (0.3)	16/3488 (0.5)	
Possibly related	106/1748 (6.1)	69/1740 (4.0)	175/3488 (5.0)	
Probably not relevant	436/1748 (24.9)	410/1740 (23.6)	846/3488 (24.3)	
Definitely irrelevant	1176/1748 (67.3)	1241/1740 (71.3)	2417/3488 (69.3)	
Unable to determine	20/1748 (1.1)	14/1740 (0.8)	34/3488 (1.0)	
Serious Adverse Event	507[#] 338/815 (41.5)	541[#] 358/826 (43.3)	1048[#] 696/1641 (42.4)	0.44
Relation to treatment				
Definitely related	4/507 (0.8)	0/541 (0.0)	4/1048 (0.4)	
Possibly related	5/507 (1.0)	5/541 (0.9)	10/1048 (1.0)	
Probably not relevant	69/507 (13.6)	53/541 (9.8)	122/1048 (11.6)	
Definitely irrelevant	427/507 (84.2)	481/541 (88.9)	908/1048 (86.6)	
Unable to determine	2/507 (0.4)	2/541 (0.4)	4/1048 (0.4)	
Adverse Event of Special Interest	116[#] 111/815 (13.6)	81[#] 78/826 (9.4)	197[#] 189/1641 (11.5)	0.01
Relation to treatment				
Definitely related	3/116 (2.6)	2/81 (2.5)	5/197 (2.5)	
Possibly related	55/116 (47.4)	26/81 (32.1)	81/197 (41.1)	
Probably not relevant	27/116 (23.3)	25/81 (30.9)	52/197 (26.4)	
Definitely irrelevant	29/116 (25.0)	25/81 (30.9)	54/197 (27.4)	
Unable to determine	2/116 (1.7)	3/81 (3.7)	5/197 (2.5)	
Haematoma enlargement (>6 mL or33%)	18[#] 18/815 (2.2)	14[#] 14/826 (1.7)	32[#] 32/1641 (2.0)	

Classification	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)	p value
Relation to treatment				
Definitely related	1/18 (5.6)	0/14 (0.0)	1/32 (3.1)	
Possibly related	0/18 (0.0)	0/14 (0.0)	0/32 (0.0)	
Probably not relevant	3/18 (16.7)	4/14 (28.6)	7/32 (21.9)	
Definitely irrelevant	14/18 (77.8)	10/14 (71.4)	24/32 (75.0)	
Unable to determine	0/18 (0.0)	0/14 (0.0)	0/32 (0.0)	
New intracranial hematoma	9[#] 9/815 (1.1)	12[#] 12/826 (1.5)	21[#] 21/1641 (1.3)	
Relation to treatment				
Definitely related	0/9 (0.0)	0/12 (0.0)	0/21 (0.0)	
Possibly related	0/9 (0.0)	0/12 (0.0)	0/21 (0.0)	
Probably not relevant	2/9 (22.2)	2/12 (16.7)	4/21 (19.0)	
Definitely irrelevant	7/9 (77.8)	10/12 (83.3)	17/21 (81.0)	
Unable to determine	0/9 (0.0)	0/12 (0.0)	0/21 (0.0)	
Diarrhoea	89[#] 86/815 (10.6)	55[#] 54/826 (6.5)	144[#] 140/1641 (8.5)	
Relation to treatment				
Definitely related	2/89 (2.2)	2/55 (3.6)	4/144 (2.8)	
Possibly related	55/89 (61.8)	26/55 (47.3)	81/144 (56.3)	
Probably not relevant	22/89 (24.7)	19/55 (34.5)	41/144 (28.5)	
Definitely irrelevant	8/89 (9.0)	5/55 (9.1)	13/144 (9.0)	
Unable to determine	2/89 (2.2)	3/55 (5.5)	5/144 (3.5)	

Data are n (%)

Table S31. Serious adverse events by condition until 90 days

Serious Adverse Event	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Respiratory, thoracic and mediastinal disorders	237 227 (27.9)	250 233 (28.2)	487 460 (28.0)
Pneumonia	220 218 (26.7)	228 228 (27.6)	448 446 (27.2)
Acute respiratory failure	15 15 (1.8)	18 17(2.0)	33 32 (2.0)
Haemoptysis	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Pleural effusion	1 1 (0.1)	1 1 (0.1)	2 2 (0.1)
Pulmonary embolism	0 0 (0.0)	3 3 (0.4)	3 3 (0.2)
Cardiac disorders	81 78 (9.6)	94 92 (11.1)	175 170 (10.4)
Cardiac arrest	76 75 (9.2)	85 85 (10.3)	161 160 (9.8)
Cardiac failure	3 3 (0.4)	2 2 (0.2)	5 5 (0.3)
Atrial fibrillation	2 2 (0.2)	2 2 (0.2)	4 4 (0.2)
Acute myocardial infarction	0 0 (0.0)	2 2 (0.2)	2 2 (0.2)
Acute respiratory failure	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Supraventricular tachycardia	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Ventricular fibrillation	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Vascular disorders	52 50 (6.1)	58 52 (6.3)	110 102 (6.2)
Deep venous thrombosis	42 41 (5.0)	40 38 (4.6)	82 79 (4.8)
Anaemia	9 9 (1.1)	10 9 (1.1)	19 18 (1.1)
Leg ulcer	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Coagulopathy	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Leukcopaenia	0 0 (0.0)	2 2 (0.2)	2 2 (0.1)
Thrombocytopaenia	0 0 (0.0)	5 5 (0.6)	5 5 (0.3)
Nervous system disorders	53 47 (5.8)	61 54 (6.5)	114 101 (6.2)
Intracerebral haemorrhage	14 13 (1.6)	14 14 (1.7)	28 27 (1.6)
Hydrocephalus	12 12 (1.5)	11 11 (1.3)	23 23 (1.4)
Intracerebral haemorrhage	10 10 (1.2)	14 14 (1.7)	24 24 (1.5)

Serious Adverse Event	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Raised intracranial pressure	6 6 (0.7)	7 7 (0.8)	13 13 (0.8)
Acute ischaemic stroke	2 2 (0.2)	2 2 (0.2)	4 4 (0.2)
Epilepsy	2 2 (0.2)	4 4 (0.5)	6 6 (0.4)
Intracranial haemorrhage	2 2 (0.2)	2 2 (0.2)	4 4 (0.2)
Acute stroke undefined	1 1 (0.1)	1 1 (0.1)	2 2 (0.1)
Acute subdural haematoma	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Intraventricular haemorrhage	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Ischaemic stroke	1 1 (0.1)	4 4 (0.5)	5 5 (0.3)
Subarachnoid haemorrhage	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Cognitive impairment	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Raise intracranial pressure	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Infections and infestations	37 35 (4.3)	36 36 (4.4)	73 71 (4.3)
Meningitis	24 24 (2.9)	30 30 (3.6)	54 54 (3.3)
Septicaemia	7 7 (0.9)	0 0 (0.0)	7 7 (0.4)
Sepsis	4 4 (0.5)	5 5 (0.6)	9 9 (0.5)
Septicaemia	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Urinary tract infection	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Anaphylactic shock	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Gastrointestinal disorders	26 25 (3.1)	27 26 (3.1)	53 51 (3.1)
Abnormal liver function	11 11 (1.3)	12 12 (1.5)	23 23 (1.4)
Upper gastrointestinal bleeding	8 8 (1.0)	11 11 (1.3)	19 19 (1.2)
Upper gastrointestinal bleeding	4 4 (0.5)	2 2 (0.2)	6 6 (0.4)
Diaorrhea	2 2 (0.2)	1 1 (0.1)	3 3 (0.2)
Gastroesophageal reflux	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Acute liver failure	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Metabolism and nutrition disorders	16 12 (1.5)	8 7 (0.8)	24 19 (1.2)

Serious Adverse Event	FYTF-919 (N=815)	Placebo (N=826)	Overall (N=1641)
Multiple organ failure	3 3 (0.4)	1 1 (0.1)	4 4 (0.2)
Electrolyte imbalance	2 2 (0.2)	0 0 (0.0)	2 2 (0.1)
Hypoalbuminaemia	2 2 (0.2)	1 1 (0.1)	3 3 (0.2)
Hypocalcaemia	2 2 (0.2)	0 0 (0.0)	2 2 (0.1)
Malnutrition	2 2 (0.2)	1 1 (0.1)	3 3 (0.2)
Metabolic alkalosis	2 2 (0.2)	0 0 (0.0)	2 2 (0.1)
Acute respiratory failure	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Hypokaleamia	1 1 (0.1)	3 3 (0.4)	4 4 (0.2)
Hyponatraemia	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Hyperkalaemia	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Hypernatraemia	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Renal and urinary disorders	3 3 (0.4)	6 6 (0.7)	9 9 (0.5)
Acute renal failure	3 3 (0.4)	6 6 (0.7)	9 9 (0.5)
Endocrine disorders	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Central diabetes insipidus	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Psychiatric disorders	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Anxiety	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Injury, poisoning and procedural complications	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Fracture	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)

Table S32. Adverse Events in the per protocol population until 90 days

Adverse Event	FYTF-919 (N = 769)	Placebo (N = 777)	Overall (N = 1546)	p value
Adverse Event	1679[#] 621/769 (80.8)	1671[#] 628/777 (80.8)	3350[#] 1249/1546 (80.8)	0.97
Relation to treatment				
Definitely related	10/1667 (0.6)	6/1661 (0.4)	16/3328 (0.5)	
Possibly related	100/1667 (6.0)	68/1661 (4.1)	168/3328 (5.0)	
probably not relevant	412/1667 (24.7)	386/1661 (23.2)	798/3328 (24.0)	
Definitely irrelevant	1127/1667 (67.6)	1187/1661 (71.5)	2314/3328 (69.5)	
Unable to determine	18/1667 (1.1)	14/1661 (0.8)	32/3328 (1.0)	
Serious Adverse Event	478[#] 322/769 (41.9)	513[#] 341/777 (43.9)	991[#] 663/1546 (42.9)	0.42
Relation to treatment				
Definitely related	4/478 (0.8)	0/513 (0.0)	4/991 (0.4)	
Possibly related	5/478 (1.0)	5/513 (1.0)	10/991 (1.0)	
probably not relevant	63/478 (13.2)	49/513 (9.6)	112/991 (11.3)	
Definitely irrelevant	404/478 (84.5)	457/513 (89.1)	861/991 (86.9)	
Unable to determine	2/478 (0.4)	2/513 (0.4)	4/991 (0.4)	
Adverse Event of Special Interest	108[#] 105/769 (13.7)	78[#] 75/777 (9.7)	186[#] 180/1546 (11.6)	0.01
Relation to treatment				
Definitely related	3/108 (2.8)	2/78 (2.6)	5/186 (2.7)	
Possibly related	53/108 (49.1)	26/78 (33.3)	79/186 (42.5)	
probably not relevant	23/108 (21.3)	23/78 (29.5)	46/186 (24.7)	
Definitely irrelevant	28/108 (25.9)	24/78 (30.8)	52/186 (28.0)	
Unable to determine	1/108 (0.9)	3/78 (3.8)	4/186 (2.2)	

Adverse Event	FYTF-919 (N = 769)	Placebo (N = 777)	Overall (N = 1546)	p value
Hematoma enlargement (>6mL or33)	17[#] 17/769 (2.2)	13[#] 13/777 (1.7)	30[#] 30/1546 (1.9)	
Relation to treatment				
Definitely related	1/17 (5.9)	0/13 (0.0)	1/30 (3.3)	
Possibly related	0/17 (0.0)	0/13 (0.0)	0/30 (0.0)	
probably not relevant	3/17 (17.6)	3/13 (23.1)	6/30 (20.0)	
Definitely irrelevant	13/17 (76.5)	10/13 (76.9)	23/30 (76.7)	
Unable to determine	0/17 (0.0)	0/13 (0.0)	0/30 (0.0)	
New intracranial hematoma	9[#] 9/769 (1.2)	12[#] 12/777 (1.5)	21[#] 21/1546 (1.4)	
Relation to treatment				
Definitely related	0/9 (0.0)	0/12 (0.0)	0/21 (0.0)	
Possibly related	0/9 (0.0)	0/12 (0.0)	0/21 (0.0)	
probably not relevant	2/9 (22.2)	2/12 (16.7)	4/21 (19.0)	
Definitely irrelevant	7/9 (77.8)	10/12 (83.3)	17/21 (81.0)	
Unable to determine	0/9 (0.0)	0/12 (0.0)	0/21 (0.0)	
Diarrhoea	82[#] 81/769 (10.5)	53[#] 52/777 (6.7)	135[#] 133/1546 (8.6)	
Relation to treatment				
Definitely related	2/82 (2.4)	2/53 (3.8)	4/135 (3.0)	
Possibly related	53/82 (64.6)	26/53 (49.1)	79/135 (58.5)	
probably not relevant	18/82 (22.0)	18/53 (34.0)	36/135 (26.7)	
Definitely irrelevant	8/82 (9.8)	4/53 (7.5)	12/135 (8.9)	
Unable to determine	1/82 (1.2)	3/53 (5.7)	4/135 (3.0)	

Table S33.2 Adverse event terms in the per protocol population until 90 days

Serious Adverse Event	FYTF-919 (N = 769)	Placebo (N = 777)	Overall (N = 1546)
AE SOC/PT term			
Respiratory, thoracic and mediastinal disorders	223 215 (28.0)	241 226 (29.1)	464 441 (28.5)
Pneumonia	207 206 (26.8)	221 221 (28.4)	428 427 (27.6)
Acute respiratory failure	12 12 (1.6)	7 7 (0.9)	19 19 (1.2)
Acute respiratory failure	2 2 (0.3)	9 8 (1.0)	11 10 (0.6)
Haemoptysis	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Pleural effusion	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Acute respiratory failure	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Pulmonary embolism	0 0 (0.0)	3 3 (0.4)	3 3 (0.2)
Cardiac disorders	74 71 (9.2)	84 82 (10.6)	158 153 (9.9)
Cardiac arrest	70 69 (9.0)	75 75 (9.7)	145 144 (9.3)
Atrial fibrillation	2 2 (0.3)	2 2 (0.3)	4 4 (0.3)
Cardiac failure	2 2 (0.3)	2 2 (0.3)	4 4 (0.3)
Acute myocardial infarction	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Acute myocardial infarction	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Acute respiratory failure	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Supraventricular tachycardia	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Ventricular fibrillation	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Vascular disorders	51 49 (6.4)	57 51 (6.6)	108 100 (6.5)
Deep venous thrombosis	42 41 (5.3)	39 37 (4.8)	81 78 (5.0)
Anaemia	8 8 (1.0)	10 9 (1.2)	18 17 (1.1)
Leg ulcer	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)

Serious Adverse Event	FYTF-919 (N = 769)	Placebo (N = 777)	Overall (N = 1546)
Coagulopathy	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Leukcopaenia	0 0 (0.0)	2 2 (0.3)	2 2 (0.1)
Thrombocytopaenia	0 0 (0.0)	5 5 (0.6)	5 5 (0.3)
Nervous system disorders	49 43 (5.6)	57 50 (6.4)	106 93 (6.0)
Intracerebral haemorrhage	14 13 (1.7)	13 13 (1.7)	27 26 (1.7)
Hydrocephalus	10 10 (1.3)	10 10 (1.3)	20 20 (1.3)
Intracerebral haemorrhage	10 10 (1.3)	13 13 (1.7)	23 23 (1.5)
Raised intracranial pressure	6 6 (0.8)	7 7 (0.9)	13 13 (0.8)
Acute ischaemic stroke	2 2 (0.3)	2 2 (0.3)	4 4 (0.3)
Epilepsy	2 2 (0.3)	3 3 (0.4)	5 5 (0.3)
Acute subdural haematoma	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Intracranial haemorrhage	1 1 (0.1)	2 2 (0.3)	3 3 (0.2)
Intraventricular haemorrhage	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Ischaemic stroke	1 1 (0.1)	4 4 (0.5)	5 5 (0.3)
Subarachnoid haemorrhage	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Acute stroke undefined	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Cognitive impairment	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Raised intracranial pressure	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Infections and infestations	37 35 (4.6)	36 36 (4.6)	73 71 (4.6)
Meningitis	24 24 (3.1)	30 30 (3.9)	54 54 (3.5)
Septicaemia	7 7 (0.9)	0 0 (0.0)	7 7 (0.5)
Sepsis	4 4 (0.5)	5 5 (0.6)	9 9 (0.6)
Septicaemia	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Urinary tract infection	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)

Serious Adverse Event	FYTF-919 (N = 769)	Placebo (N = 777)	Overall (N = 1546)
Anaphylactic shock	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Gastrointestinal disorders	24 23 (3.0)	26 25 (3.2)	50 48 (3.1)
Abnormal liver function	10 10 (1.3)	12 12 (1.5)	22 22 (1.4)
Upper gastrointestinal bleeding	7 7 (0.9)	10 10 (1.3)	17 17 (1.1)
Uppe rgastrointestinal bleeding	4 4 (0.5)	2 2 (0.3)	6 6 (0.4)
Diaorrhea	2 2 (0.3)	1 1 (0.1)	3 3 (0.2)
Gastroesophageal reflux	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Acute liver failure	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Metabolism and nutrition disorders	16 12 (1.6)	7 6 (0.8)	23 18 (1.2)
Multiple organ failure	3 3 (0.4)	1 1 (0.1)	4 4 (0.3)
Electrolyte imbalance	2 2 (0.3)	0 0 (0.0)	2 2 (0.1)
Hypoalbuminaemia	2 2 (0.3)	1 1 (0.1)	3 3 (0.2)
Hypocalcaemia	2 2 (0.3)	0 0 (0.0)	2 2 (0.1)
Malnutrition	2 2 (0.3)	0 0 (0.0)	2 2 (0.1)
Metabolic alkalosis	2 2 (0.3)	0 0 (0.0)	2 2 (0.1)
Acute respiratory failure	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Hypokalaemia	1 1 (0.1)	3 3 (0.4)	4 4 (0.3)
Hyponatraemia	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Hyperkalaemia	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Hypernatraemia	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Renal and urinary disorders	2 2 (0.3)	4 4 (0.5)	6 6 (0.4)
Acute renal failure	2 2 (0.3)	4 4 (0.5)	6 6 (0.4)

Serious Adverse Event	FYTF-919 (N = 769)	Placebo (N = 777)	Overall (N = 1546)
Endocrine disorders	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Central diabetes insipidus	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Psychiatric disorders	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Anxiety	1 1 (0.1)	0 0 (0.0)	1 1 (0.1)
Injury, poisoning and procedural complications	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)
Fracture	0 0 (0.0)	1 1 (0.1)	1 1 (0.1)

Table S34. List of1 deaths by Day 180

Subject ID	Treatment group	Days from randomisation to death	Death reason
1001-0008	FYTF-919	19	Nervous system damage from this stroke
1001-0014	Placebo	163	Other - Unknown
1001-0030	FYTF-919	34	Nervous system damage from this stroke
1001-0038	Placebo	28	Cardiovascular disease
1001-0040	Placebo	21	Other - Respiratory failure
1001-0042	FYTF-919	9	Nervous system damage from this stroke
1001-0044	FYTF-919	50	Other - Unknown
1001-0049	FYTF-919	103	Cardiovascular disease
1002-0002	FYTF-919	9	Other - Unknown
1002-0019	Placebo	25	Nervous system damage from this stroke
1002-0025	Placebo	17	Nervous system damage from this stroke
1002-0027	FYTF-919	16	Nervous system damage from this stroke
1003-0007	FYTF-919	92	Nervous system damage from this stroke
1003-0011	FYTF-919	4	Other - Unknown
1003-0013	Placebo	6	Other - Respiratory failure
1003-0014	Placebo	15	Nervous system damage from this stroke
1003-0018	FYTF-919	117	Lung infection
1003-0023	FYTF-919	5	Stroke recurrence
1003-0024	FYTF-919	179	Cardiovascular disease
1003-0025	FYTF-919	73	Lung infection
1003-0030*	FYTF-919	92	Lung infection
1003-0033	FYTF-919	8	Nervous system damage from this stroke
1003-0034	Placebo	116	Other - Unknown
1003-0037*	Placebo	98	Lung infection
1003-0046	FYTF-919	58	Lung infection

Subject ID	Treatment group	Days from randomisation to death	Death reason
1003-0051*	FYTF-919	13	Lung infection
1003-0053	FYTF-919	57	Lung infection
1003-0057	Placebo	42	Lung infection
1003-0059	FYTF-919	31	Lung infection
1003-0067	FYTF-919	37	Other - Unknown
1003-0076	Placebo	16	Nervous system damage from this stroke
1003-0081	Placebo	113	Lung infection
1003-0087	FYTF-919	32	Lung infection
1004-0010	Placebo	80	Nervous system damage from this stroke
1005-0055	Placebo	85	Nervous system damage from this stroke
1005-0067	FYTF-919	8	Nervous system damage from this stroke
1005-0112	FYTF-919	6	Nervous system damage from this stroke
1006-0001*	FYTF-919		Other - Unknown
1006-0008*	FYTF-919		Other - Unknown
1006-0013*	Placebo		Other - Unknown
1006-0014*	FYTF-919		Nervous system damage from this stroke
1006-0018	Placebo	13	Nervous system damage from this stroke
1006-0029	Placebo	5	Nervous system damage from this stroke
1006-0036	Placebo	4	Other - Circulatory failure and Respiratory failure
1006-0059	Placebo	16	Other - Unknown
1006-0063	FYTF-919	7	Nervous system damage from this stroke
1006-0070	Placebo	14	Lung infection
1006-0072	FYTF-919	15	Other - Unknown
1006-0073	FYTF-919	97	Other - Respiratory failure
1006-0077	FYTF-919	11	Nervous system damage from this stroke
1006-0084	FYTF-919	27	Other - Heart failure
1006-0109	Placebo	64	Other - Unknown

Subject ID	Treatment group	Days from randomisation to death	Death reason
1006-0110	Placebo	25	Other - Unknown
1006-0125	Placebo	4	Nervous system damage from this stroke
1006-0132	Placebo	29	Nervous system damage from this stroke
1006-0137	Placebo	27	Other - Unknown
1006-0138	FYTF-919	15	Nervous system damage from this stroke
1006-0139	FYTF-919	25	Other - Unknown
1006-0141	Placebo	32	Other - Unknown
1006-0144	Placebo	121	Other - Unknown
1006-0145	Placebo	31	Other - Unknown
1006-0147	FYTF-919	172	Other - Unknown
1006-0154	FYTF-919	3	Nervous system damage from this stroke
1006-0169	FYTF-919	8	Other - Unknown
1006-0178	Placebo	126	Nervous system damage from this stroke
1006-0194	FYTF-919	12	Other - Unknown
1006-0201	Placebo	44	Other - Unknown
1006-0203	Placebo	8	Nervous system damage from this stroke
1007-0012	Placebo	115	Nervous system damage from this stroke
1007-0016	FYTF-919	38	Nervous system damage from this stroke
1007-0017	FYTF-919	6	Cardiovascular disease
1007-0036	FYTF-919	83	Lung infection
1007-0063	FYTF-919	10	Nervous system damage from this stroke
1007-0070	FYTF-919	105	Nervous system damage from this stroke
1007-0075	Placebo	136	Nervous system damage from this stroke
1007-0076	FYTF-919	98	Lung infection
1009-0001	FYTF-919	11	Nervous system damage from this stroke
1009-0008	Placebo	130	Other - Unknown
1009-0041	Placebo	76	Nervous system damage from this stroke

Subject ID	Treatment group	Days from randomisation to death	Death reason
1009-0047	FYTF-919	82	Nervous system damage from this stroke
1009-0052	Placebo	3	Nervous system damage from this stroke
1010-0021	FYTF-919	152	Other - Unknown
1010-0036	Placebo	50	Lung infection
1011-0003	FYTF-919	10	Nervous system damage from this stroke
1011-0004	FYTF-919	60	Nervous system damage from this stroke
1011-0010	Placebo	36	Nervous system damage from this stroke
1011-0017	Placebo	17	Other - Unknown
1011-0021	FYTF-919	28	Nervous system damage from this stroke
1011-0032	FYTF-919	9	Other - Unknown
1011-0033	Placebo	15	Nervous system damage from this stroke
1011-0036	FYTF-919	43	Nervous system damage from this stroke
1011-0040*	Placebo	94	Other - Unknown
1011-0042	Placebo	7	Nervous system damage from this stroke
1011-0043	FYTF-919	10	Nervous system damage from this stroke
1011-0046	Placebo	23	Nervous system damage from this stroke
1011-0050	FYTF-919	12	Nervous system damage from this stroke
1011-0056	Placebo	37	Nervous system damage from this stroke
1011-0068*	FYTF-919	93	Other - Unknown
1011-0080*	FYTF-919	8	Nervous system damage from this stroke
1011-0081	FYTF-919	13	Nervous system damage from this stroke
1011-0094	Placebo	13	Nervous system damage from this stroke
1012-0007	Placebo	4	Other - Unknown
1012-0009	FYTF-919	6	Nervous system damage from this stroke
1012-0011	Placebo	3	Nervous system damage from this stroke
1012-0015	Placebo	85	Other - Unknown
1012-0021	FYTF-919	44	Nervous system damage from this stroke

Subject ID	Treatment group	Days from randomisation to death	Death reason
1012-0023	FYTF-919	15	Other - Unknown
1012-0029	Placebo	16	Nervous system damage from this stroke
1012-0038	Placebo	92	Other - Multiple organ failure
1012-0041	Placebo	4	Other - Unknown
1012-0042	FYTF-919	2	Other - Unknown
1012-0043	Placebo	48	Other - Unknown
1013-0001*	FYTF-919	28	Other - Sudden death
1013-0008	Placebo	14	Other - Respiratory failure
1013-0024	Placebo	5	Nervous system damage from this stroke
1014-0004	FYTF-919	10	Nervous system damage from this stroke
1014-0008*	FYTF-919	30	Other - Unknown
1014-0009	FYTF-919	2	Nervous system damage from this stroke
1014-0011	Placebo	30	Lung infection
1014-0012	FYTF-919	11	Nervous system damage from this stroke
1014-0015	Placebo	93	Other - Unknown
1014-0016	Placebo	12	Nervous system damage from this stroke
1014-0017	Placebo	4	Lung infection
1014-0018	FYTF-919	10	Other - Multiple organ failure
1014-0019	FYTF-919	7	Lung infection
1014-0020	Placebo	19	Lung infection
1015-0012	Placebo	15	Nervous system damage from this stroke
1015-0013	Placebo	23	Stroke recurrence
1015-0025	FYTF-919	19	Other - Respiratory failure
1015-0027	Placebo	17	Other - Unknown
1015-0035	Placebo	21	Lung infection
1015-0036	Placebo	2	Stroke recurrence
1015-0045	Placebo	12	Nervous system damage from this stroke

Subject ID	Treatment group	Days from randomisation to death	Death reason
1015-0046	FYTF-919	22	Other - Unknown
1015-0050	Placebo	6	Nervous system damage from this stroke
1015-0052	FYTF-919	10	Nervous system damage from this stroke
1015-0058	FYTF-919	136	Nervous system damage from this stroke
1016-0004	FYTF-919	64	Other - Unknown
1016-0008	Placebo	24	Lung infection
1016-0010	Placebo	155	Lung infection
1016-0015	Placebo	87	Lung infection
1016-0028	Placebo	9	Cardiovascular disease
1016-0029	Placebo	7	Nervous system damage from this stroke
1017-0008	Placebo	5	Nervous system damage from this stroke
1017-0012	Placebo	101	Stroke recurrence
1017-0018	Placebo	3	Nervous system damage from this stroke
1017-0054	Placebo	4	Lung infection
1017-0063	FYTF-919	3	Nervous system damage from this stroke
1017-0078	Placebo	39	Other - Gastrointestinal bleeding
1017-0105	Placebo	47	Other - Unknown
1017-0108	FYTF-919	5	Nervous system damage from this stroke
1017-0124	Placebo	68	Nervous system damage from this stroke
1017-0134	Placebo	15	Nervous system damage from this stroke
1017-0163	Placebo	10	Lung infection
1017-0171	Placebo	23	Lung infection
1017-0175	FYTF-919	56	Other - Septicemia
1017-0190	Placebo	93	Other - Respiratory and circulatory failure
1017-0192	FYTF-919	56	Other - Respiratory and circulatory failure
1017-0264	Placebo	7	Nervous system damage from this stroke
1017-0267	FYTF-919	90	Other - Cachectic state

Subject ID	Treatment group	Days from randomisation to death	Death reason
1017-0291	FYTF-919	13	Nervous system damage from this stroke
1017-0316	FYTF-919	10	Nervous system damage from this stroke
1017-0327	Placebo	2	Other - Respiratory and circulatory failure
1017-0333	FYTF-919	120	Stroke recurrence
1017-0338	Placebo	52	Other - Unknown
1017-0355	Placebo	167	Other - Unknown
1017-0357	FYTF-919	16	Other - Unknown
1017-0358	Placebo	13	Nervous system damage from this stroke
1017-0365	Placebo	134	Nervous system damage from this stroke
1017-0394	Placebo	3	Nervous system damage from this stroke
1019-0002	FYTF-919	6	Cardiovascular disease
1019-0013	Placebo	2	Nervous system damage from this stroke
1019-0014	Placebo	7	Nervous system damage from this stroke
1019-0020*	Placebo	31	Other - Unknown
1019-0023	Placebo	27	Lung infection
1019-0029	FYTF-919	3	Nervous system damage from this stroke
1019-0031	Placebo	174	Other - Respiratory failure
1019-0042	Placebo	5	Other - Unknown
1019-0043	FYTF-919	17	Other - Unknown
1019-0045	FYTF-919	60	Other - Unknown
1019-0046	Placebo	72	Other - Unknown
1019-0052	Placebo	80	Other - Unknown
1020-0008	Placebo	5	Nervous system damage from this stroke
1020-0010	FYTF-919	4	Nervous system damage from this stroke
1020-0014	FYTF-919	6	Nervous system damage from this stroke
1020-0034	FYTF-919	28	Nervous system damage from this stroke
1020-0039	FYTF-919	25	Other - Heart failure

Subject ID	Treatment group	Days from randomisation to death	Death reason
1020-0044	FYTF-919	20	Nervous system damage from this stroke
1020-0054	Placebo	22	Other - Pulmonary embolism
1020-0059	FYTF-919	27	Other - Epilepsy
1020-0060	FYTF-919	9	Nervous system damage from this stroke
1020-0065	Placebo	27	Nervous system damage from this stroke
1020-0066	FYTF-919	3	Nervous system damage from this stroke
1020-0070	Placebo	2	Nervous system damage from this stroke
1023-0004	FYTF-919	52	Nervous system damage from this stroke
1023-0006	FYTF-919	2	Nervous system damage from this stroke
1023-0007	Placebo	164	Other - Unknown
1025-0001*	Placebo		Other - Unknown
1025-0004	FYTF-919	9	Nervous system damage from this stroke
1026-0009	Placebo	104	Other - Unknown
1026-0010	FYTF-919	6	Nervous system damage from this stroke
1026-0018*	FYTF-919	97	Other - Unknown
1026-0024	Placebo	14	Nervous system damage from this stroke
1026-0031	FYTF-919	2	Nervous system damage from this stroke
1026-0032	Placebo	29	Lung infection
1026-0036	FYTF-919	109	Stroke recurrence
1026-0042	FYTF-919	23	Lung infection
1026-0043	Placebo	13	Other - Unknown
1026-0050	FYTF-919	4	Nervous system damage from this stroke
1028-0001	Placebo	23	Other - Unknown
1028-0005	FYTF-919	12	Lung infection
1028-0006	Placebo	11	Other - Respiratory failure
1028-0009	FYTF-919	10	Other - Respiratory failure
1028-0011	FYTF-919	19	Other - Respiratory failure

Subject ID	Treatment group	Days from randomisation to death	Death reason
1028-0019	FYTF-919	11	Other - Respiratory failure
1029-0009	FYTF-919	63	Other - Gastrointestinal bleeding
1030-0003	FYTF-919	12	Nervous system damage from this stroke
1031-0006	FYTF-919	150	Nervous system damage from this stroke
1031-0040	Placebo	13	Other - Respiratory failure
1031-0051	FYTF-919	29	Nervous system damage from this stroke
1031-0052	Placebo	7	Stroke recurrence
1031-0060	FYTF-919	9	Nervous system damage from this stroke
1031-0082	FYTF-919	74	Other - Unknown
1031-0083	FYTF-919	15	Nervous system damage from this stroke

Table S35.2 List of all serious adverse events by Day 180

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1001-0001	Placebo	25NOV2021	Pneumonia	Definitely irrelevant	Recovered/Resolved
1001-0002	Placebo	01DEC2021	Pneumonia	probably not relevant	Recovered/Resolved
1001-0007	Placebo	13DEC2021	Intracranial infection	Definitely irrelevant	Recovered/Resolved
1001-0008	FYTF-919	28DEC2021	Respiratory failure	probably not relevant	death
		15DEC2021	Stroke-associated pneumonia	Definitely irrelevant	death
1001-0010	Placebo	21DEC2021	Pneumonia	probably not relevant	Recovered/Resolved
1001-0012	FYTF-919	08JAN2022	Intracranial infection	Definitely irrelevant	Recovered/resolved with sequelae
1001-0014	Placebo	21JUN2022	Death	Definitely irrelevant	death
1001-0015	FYTF-919	13JAN2022	Sepsis	Definitely irrelevant	Recovered/Resolved
1001-0022	FYTF-919	02FEB2022	Pneumonia	probably not relevant	Recovered/Resolved
1001-0027	FYTF-919	14MAR2022	Pneumonia	probably not relevant	Recovered/Resolved
		06MAR2022	Epilepsy	probably not relevant	Recovered/Resolved
1001-0030	FYTF-919	28APR2022	Death	Definitely irrelevant	death
1001-0031	FYTF-919	29MAR2022	Pneumonia	probably not relevant	Recovered/Resolved
1001-0034	FYTF-919	06MAY2022	Pneumonia	probably not relevant	Recovered/Resolved
1001-0036	Placebo	22NOV2022	Anemia	Definitely irrelevant	Recovered/Resolved
1001-0037	Placebo	08DEC2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		08DEC2022	Acute myocardial infarction	probably not relevant	Recovered/Resolved
1001-0038	Placebo	26JAN2023	Hyperkalaemia	Definitely irrelevant	death
		29JAN2023	Sepsis	Definitely irrelevant	death
		29JAN2023	Pneumonia	Definitely irrelevant	death
1001-0039	FYTF-919	09FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1001-0040	Placebo	15APR2023	Respiratory failure	Definitely irrelevant	death
1001-0041	Placebo	06APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		16APR2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
		05APR2023	Anaemia	Definitely irrelevant	Recovered/Resolved
1001-0042	FYTF-919	15APR2023	Respiratory failure	Definitely irrelevant	death
1001-0044	FYTF-919	15MAY2023	Pneumonia	Definitely irrelevant	death

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
		29JUN2023	Death	Definitely irrelevant	death
1001-0045	FYTF-919	06JUN2023	Pneumonia	probably not relevant	Recovered/Resolved
		07JUN2023	Intracranial infection	probably not relevant	Recovered/Resolved
1001-0047	FYTF-919	17JUN2023	Pneumonia	probably not relevant	Recovered/Resolved
1001-0048	Placebo	24JUL2023	Anaemia	Definitely irrelevant	Recovered/Resolved
1001-0049	FYTF-919	16NOV2023	Death	Definitely irrelevant	death
1001-0050	FYTF-919	22AUG2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1002-0001	FYTF-919	15JAN2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1002-0002	FYTF-919	18JAN2022	Pneumonia	Definitely irrelevant	death
		25JAN2022	Heart failure	Definitely irrelevant	death
1002-0004	FYTF-919	02FEB2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1002-0007	FYTF-919	11APR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		11APR2022	Intracerebral haemorrhage	Definitely irrelevant	Recovered/Resolved
1002-0008	Placebo	25MAY2022	Intracerebral haemorrhage	Definitely irrelevant	Recovered/Resolved
1002-0009	Placebo	10MAY2022	Haematoma expansion	probably not relevant	Recovered/resolved with sequelae
1002-0019	Placebo	13JAN2022	Death	Definitely irrelevant	death
1002-0024	FYTF-919	18MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1002-0025	Placebo	09APR2022	Ischaemic stroke	Definitely irrelevant	death
		11APR2022	Death	Definitely irrelevant	death
1002-0026	Placebo	01APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1002-0027	FYTF-919	24APR2023	Brain herniation	Definitely irrelevant	death
		24APR2023	Intracerebral haemorrhage	Definitely irrelevant	death
1002-0028	Placebo	13MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1002-0030	FYTF-919	21MAY2023	Haematoma expansion	Definitely irrelevant	Recovered/Resolved
1002-0032	FYTF-919	14SEP2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1002-0033	Placebo	28SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1002-0035	FYTF-919	18OCT2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1002-0036	Placebo	22OCT2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1003-0007	FYTF-919	17MAY2022	Death	probably not relevant	death

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1003-0011	FYTF-919	25MAR2022	Death	Definitely irrelevant	death
		22FEB2022	Heart failure	Definitely irrelevant	death
		23FEB2022	Hydrocephalus	Definitely irrelevant	death
1003-0012	Placebo	22FEB2022	Stroke-associated pneumonia	Definitely irrelevant	Recovered/Resolved
1003-0013	Placebo	01MAR2022	Death	probably not relevant	death
1003-0014	Placebo	10MAR2022	Death	probably not relevant	death
1003-0018	FYTF-919	18MAR2022	Intracranial infection	Definitely irrelevant	Recovered/Resolved
		03JUL2022	Death	Definitely irrelevant	death
1003-0020	Placebo	20MAR2022	Stroke-associated pneumonia	probably not relevant	Recovered/Resolved
1003-0023	FYTF-919	28MAR2022	Haematoma expansion	probably not relevant	death
		31MAR2022	Death	probably not relevant	death
		28MAR2022	Stroke-associated pneumonia	probably not relevant	death
1003-0024	FYTF-919	23SEP2022	Cardiogenic shock	Definitely irrelevant	death
		24SEP2022	Death	probably not relevant	death
1003-0025	FYTF-919	10JUN2022	Death	Definitely irrelevant	death
1003-0030	FYTF-919	11OCT2022	Death	Definitely irrelevant	death
1003-0033	FYTF-919	25JUL2022	Death	probably not relevant	death
1003-0034	Placebo	25NOV2022	Death	Definitely irrelevant	death
		09AUG2022	Pneumonia	probably not relevant	Recovered/resolved with sequelae
1003-0037	Placebo	17APR2023	Death	Definitely irrelevant	death
1003-0046	FYTF-919	07FEB2023	Death	Definitely irrelevant	death
		14DEC2022	Hydrocephalus	probably not relevant	Recovered/resolved with sequelae
1003-0051	FYTF-919	17APR2023	Death	Definitely irrelevant	death
1003-0053	FYTF-919	12FEB2023	Diarrhea	probably not relevant	Recovered/Resolved
		06APR2023	Death	probably not relevant	death
1003-0057	Placebo	17MAR2023	Acute respiratory failure	probably not relevant	Recovered/resolved with sequelae
		29MAR2023	Death	probably not relevant	death
1003-0059	FYTF-919	22MAR2023	Death	probably not relevant	death
1003-0061	FYTF-919	04MAR2023	Venous thrombosis limb	probably not relevant	Recovered/resolved with sequelae

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
		03MAR2023	Haematoma expansion	probably not relevant	Recovered/Resolved
1003-0066	FYTF-919	07MAR2023	Haematoma expansion	probably not relevant	Recovered/Resolved
1003-0067	FYTF-919	23APR2023	Death	probably not relevant	death
		15MAR2023	Stroke-associated pneumonia	probably not relevant	Recovered/Resolved
1003-0070	FYTF-919	24MAR2023	Stroke-associated pneumonia	probably not relevant	Recovered/Resolved
1003-0072	FYTF-919	24MAR2023	Stroke-associated pneumonia	probably not relevant	Recovered/Resolved
1003-0074	Placebo	14APR2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
1003-0076	Placebo	24MAR2023	Hydrocephalus	Definitely irrelevant	Recovered/resolved with sequelae
		09MAY2023	Death	Definitely irrelevant	death
1003-0077	FYTF-919	14MAY2023	Intracranial infection	probably not relevant	Recovered/Resolved
1003-0081	Placebo	08SEP2023	Death	Definitely irrelevant	death
1003-0087	FYTF-919	14OCT2023	Multiple organ failure	Definitely irrelevant	death
		08NOV2023	Death	Definitely irrelevant	death
1004-0010	Placebo	07APR2023	Death	Definitely irrelevant	death
1005-0003	Placebo	04JUN2022	Intracerebral haemorrhage	Definitely irrelevant	Recovered/resolved with sequelae
1005-0012	Placebo	06MAY2022	Venous thrombosis limb	Definitely irrelevant	Recovered/Resolved
1005-0013	FYTF-919	06MAY2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		06MAY2022	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
1005-0019	FYTF-919	23NOV2022	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1005-0020	Placebo	31JAN2023	Venous thrombosis limb	Definitely irrelevant	Recovered/Resolved
		19FEB2023	Myocardial infarction	Definitely irrelevant	Recovered/Resolved
		29JAN2023	Thrombocytopenia	Definitely irrelevant	Recovered/Resolved
		29JAN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1005-0022	Placebo	06FEB2023	Venous thrombosis deep	Definitely irrelevant	Recovered/Resolved
1005-0026	Placebo	12FEB2023	Lymphocyte count decreased	Definitely irrelevant	Recovered/Resolved
1005-0027	FYTF-919	12FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1005-0028	FYTF-919	20FEB2023	Intermuscular venous thrombosis	Definitely irrelevant	Recovered/Resolved
1005-0029	Placebo	12FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		14FEB2023	Lymphocyte count decreased	Definitely irrelevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1005-0031	Placebo	17FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		22FEB2023	Venous thrombosis deep	Definitely irrelevant	Recovered/Resolved
1005-0033	Placebo	23FEB2023	Brain herniation	Definitely irrelevant	Recovered/Resolved
		23FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1005-0037	Placebo	02MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1005-0038	Placebo	03MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1005-0040	FYTF-919	13MAR2023	Intermuscular venous thrombosis	Definitely irrelevant	Recovered/Resolved
1005-0043	Placebo	20MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		07APR2023	Venous thrombosis deep	Definitely irrelevant	Recovered/Resolved
		12JUL2023	Intracerebral haemorrhage	Definitely irrelevant	Recovered/resolved with sequelae
1005-0046	Placebo	25MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1005-0047	Placebo	07APR2023	Pulmonary embolism	Definitely irrelevant	Recovered/Resolved
		13APR2023	Hepatic function abnormal	Definitely irrelevant	Recovered/Resolved
		05APR2023	Venous thrombosis deep	Definitely irrelevant	Recovered/Resolved
		24MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		06APR2023	Atrial fibrillation	Definitely irrelevant	Recovered/Resolved
		06APR2023	Cardiac insufficiency	Definitely irrelevant	Recovered/Resolved
1005-0048	Placebo	31MAR2023	Renal insufficiency	Definitely irrelevant	Recovered/Resolved
		31MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1005-0051	Placebo	01MAY2023	Bacterial pneumonia	Definitely irrelevant	Recovered/Resolved
1005-0055	Placebo	15MAY2023	Pneumonia	Definitely irrelevant	death
1005-0056	FYTF-919	11MAY2023	Venous thrombosis limb	Definitely irrelevant	Recovered/Resolved
1005-0061	Placebo	05JUN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		28JUN2023	Thrombocytopenia	Definitely irrelevant	Recovered/Resolved
1005-0067	FYTF-919	13AUG2023	Death	Definitely irrelevant	death
		08AUG2023	Intracranial infection	Definitely irrelevant	death
		13AUG2023	Venous thrombosis deep	Definitely irrelevant	death
1005-0094	FYTF-919	02NOV2023	Hydrocephalus	Definitely irrelevant	Recovered/Resolved
1005-0098	Placebo	06FEB2024	Intracerebral haemorrhage	Definitely irrelevant	Recovered/resolved with sequelae

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1005-0102	Placebo	15NOV2023	Hypokalaemia	Definitely irrelevant	Recovered/Resolved
1005-0111	FYTF-919	14DEC2023	Hepatic function abnormal	Definitely irrelevant	Recovered/Resolved
1005-0112	FYTF-919	18DEC2023	Venous thrombosis deep	Definitely irrelevant	death
		18DEC2023	Cardiogenic shock	Definitely irrelevant	death
		18DEC2023	Septic shock	Definitely irrelevant	death
1005-0113	FYTF-919	22DEC2023	Venous thrombosis limb	Definitely irrelevant	Recovered/resolved with sequelae
1005-0116	FYTF-919	03JAN2024	Venous thrombosis limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0001	FYTF-919		Death	Unable to determine	death
1006-0006	Placebo	12DEC2021	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
		12DEC2021	Intracranial infection	Definitely irrelevant	Recovered/resolved with sequelae
		19DEC2021	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0008	FYTF-919		Death	Definitely irrelevant	death
		25DEC2021	Intracranial infection	Definitely irrelevant	death
		14DEC2021	Hydrocephalus	Definitely irrelevant	death
		12DEC2021	Pneumonia	Definitely irrelevant	death
1006-0009	Placebo	18DEC2021	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
		18DEC2021	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
1006-0010	FYTF-919	29DEC2021	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0012	FYTF-919	01JAN2022	Intracranial infection	Definitely irrelevant	Recovered/resolved with sequelae
1006-0013	Placebo	03JAN2022	Sepsis	Definitely irrelevant	death
		01JAN2022	Pneumonia	probably not relevant	death
			Death	Definitely irrelevant	death
1006-0014	FYTF-919		Death	Definitely irrelevant	death
		30DEC2021	Respiratory failure	Definitely irrelevant	death
1006-0015	FYTF-919	09JAN2022	Venous thrombosis deep limb	probably not relevant	Recovered/resolved with sequelae
		02JAN2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1006-0018	Placebo	09JAN2022	Intracranial infection	Definitely irrelevant	death
			Death	Definitely irrelevant	death
1006-0020	Placebo	11JAN2022	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
		14JAN2022	Intracranial infection	Definitely irrelevant	Recovered/resolved with sequelae
1006-0029	Placebo	11FEB2022	Brain herniation	Definitely irrelevant	death
		09FEB2022	Pneumonia	Definitely irrelevant	death
1006-0031	Placebo	20FEB2022	Intracranial infection	Definitely irrelevant	Recovered/Resolved
1006-0035	FYTF-919	09MAR2022	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0036	Placebo	09MAR2022	Death	Definitely irrelevant	death
1006-0040	Placebo	20MAR2022	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0044	FYTF-919	24MAR2022	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0045	Placebo	22MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1006-0050	FYTF-919	10MAY2022	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
		08APR2022	Intracranial infection	Definitely irrelevant	Recovered/Resolved
1006-0051	Placebo	28APR2022	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
1006-0052	Placebo	17APR2022	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0055	FYTF-919	09MAY2022	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0057	Placebo	19MAY2022	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0059	Placebo	30JUN2022	Renal insufficiency	probably not relevant	death
		09JUL2022	Venous thrombosis deep limb	Definitely irrelevant	death
		02JUL2022	Pneumonia	Definitely irrelevant	death
1006-0060	Placebo	09SEP2022	Hepatic function abnormal	probably not relevant	Recovered/Resolved
1006-0061	FYTF-919	04AUG2022	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0062	Placebo	11AUG2022	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
		09AUG2022	Intracranial infection	Definitely irrelevant	Recovered/resolved with sequelae
1006-0064	Placebo	03SEP2022	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
		16AUG2022	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0065	FYTF-919	25SEP2022	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
		29AUG2022	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0067	Placebo	19NOV2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1006-0068	Placebo	08DEC2022	Pneumonia	probably not relevant	Recovered/Resolved
1006-0069	FYTF-919	10DEC2022	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1006-0070	Placebo	23DEC2022	Death	Definitely irrelevant	death
1006-0071	Placebo	11DEC2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1006-0072	FYTF-919	11FEB2023	Death	Definitely irrelevant	death
1006-0073	FYTF-919	07MAY2023	Death	Definitely irrelevant	death
1006-0075	FYTF-919	20FEB2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
		14FEB2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0077	FYTF-919	12FEB2023	Pneumonia	Definitely irrelevant	death
1006-0079	Placebo	06MAR2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0083	Placebo	12MAR2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
1006-0084	FYTF-919	08MAR2023	Pneumonia	probably not relevant	death
		03APR2023	Death	Definitely irrelevant	death
1006-0085	Placebo	01APR2023	Venous thrombosis limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0087	FYTF-919	13MAR2023	Fever	probably not relevant	Recovered/Resolved
1006-0088	Placebo	20MAR2023	Venous thrombosis limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0089	FYTF-919	25MAR2023	Hepatic function abnormal	probably not relevant	Recovered/resolved with sequelae
1006-0090	FYTF-919	23MAR2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0091	FYTF-919	23MAR2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0093	Placebo	10APR2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
1006-0094	FYTF-919	12APR2023	Pneumonia	probably not relevant	Recovered/resolved with sequelae
		19APR2023	Intracranial infection	probably not relevant	Recovered/resolved with sequelae
1006-0097	Placebo	23APR2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
		25APR2023	Intracranial infection	Definitely irrelevant	Recovered/resolved with sequelae
		23APR2023	Hepatic function abnormal	probably not relevant	Recovered/Resolved
1006-0098	Placebo	25APR2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
		20APR2023	Hypoxemia	Definitely irrelevant	Recovered/Resolved
1006-0099	Placebo	28APR2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
		21APR2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0100	FYTF-919	01MAY2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
1006-0101	FYTF-919	30APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
		04MAY2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
1006-0102	FYTF-919	04MAY2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
		09MAY2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0105	FYTF-919	06MAY2023	Brain herniation	Definitely irrelevant	Recovered/resolved with sequelae
		06MAY2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
1006-0109	Placebo	15MAY2023	Pneumonia	Definitely irrelevant	death
		17JUL2023	Death	Definitely irrelevant	death
1006-0110	Placebo	15JUN2023	Death	probably not relevant	death
		23MAY2023	Brain herniation	Definitely irrelevant	death
1006-0113	FYTF-919	04JUN2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0118	FYTF-919	07JUN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1006-0119	FYTF-919	09JUN2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0121	FYTF-919	17JUN2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0122	Placebo	20JUN2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0124	FYTF-919	26JUN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		29JUN2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
1006-0125	Placebo	04JUL2023	Death	Definitely irrelevant	death
1006-0126	FYTF-919	05JUL2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0127	Placebo	09JUL2023	Intracranial infection	Definitely irrelevant	Recovered/resolved with sequelae
1006-0128	FYTF-919	13JUL2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0130	Placebo	25JUL2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
		22JUL2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0132	Placebo	24AUG2023	Death	Definitely irrelevant	death
		30JUL2023	Intracranial infection	Definitely irrelevant	death
1006-0134	FYTF-919	15AUG2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
1006-0136	Placebo	18AUG2023	Sepsis	Definitely irrelevant	Recovered/resolved with sequelae
		08SEP2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0137	Placebo	12AUG2023	Venous thrombosis deep limb	probably not relevant	death
		12AUG2023	Pneumonia	Definitely irrelevant	death

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
		12AUG2023	Venous thrombosis deep limb	Definitely irrelevant	death
1006-0138	FYTF-919	19AUG2023	Intracranial infection	Definitely irrelevant	death
		28AUG2023	Death	Definitely irrelevant	death
1006-0139	FYTF-919	17AUG2023	Pneumonia	Definitely irrelevant	death
		20AUG2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
		10SEP2023	Death	Definitely irrelevant	death
1006-0141	Placebo	20SEP2023	Death	Definitely irrelevant	death
1006-0142	FYTF-919	24AUG2023	Venous thrombosis deep limb	probably not relevant	Recovered/resolved with sequelae
		10SEP2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
1006-0143	FYTF-919	29AUG2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0144	Placebo	02SEP2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
		19FEB2024	Death	Definitely irrelevant	death
1006-0145	Placebo	28AUG2023	Pneumonia	Definitely irrelevant	death
		27SEP2023	Death	Definitely irrelevant	death
1006-0146	FYTF-919	01SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1006-0147	FYTF-919	04SEP2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
		21FEB2024	Death	Definitely irrelevant	death
1006-0148	Placebo	08SEP2023	Intracranial infection	Definitely irrelevant	Recovered/resolved with sequelae
1006-0149	Placebo	04SEP2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0150	FYTF-919	09SEP2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
1006-0151	Placebo	12SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		19SEP2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0152	Placebo	20SEP2023	Intracranial infection	Definitely irrelevant	Recovered/resolved with sequelae
1006-0153	Placebo	21SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1006-0154	FYTF-919	22SEP2023	Death	Definitely irrelevant	death
1006-0155	FYTF-919	22SEP2023	Intracranial infection	Definitely irrelevant	Recovered/resolved with sequelae
1006-0157	Placebo	23SEP2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
1006-0159	Placebo	28SEP2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0160	FYTF-919	27SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1006-0161	FYTF-919	16NOV2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
		08OCT2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0162	Placebo	11OCT2023	Intracranial infection	Definitely irrelevant	Recovered/resolved with sequelae
1006-0163	Placebo	09OCT2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0164	FYTF-919	10OCT2023	Anemia	probably not relevant	Recovered/Resolved
1006-0166	FYTF-919	18OCT2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0167	Placebo	19OCT2023	Intracranial infection	Definitely irrelevant	Recovered/resolved with sequelae
1006-0169	FYTF-919	25OCT2023	Death	Definitely irrelevant	death
1006-0171	FYTF-919	23OCT2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1006-0172	Placebo	25OCT2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0173	Placebo	25OCT2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0174	FYTF-919	26OCT2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0175	FYTF-919	01NOV2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1006-0176	FYTF-919	30OCT2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
		05NOV2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
1006-0178	Placebo	14NOV2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
		28OCT2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
		01MAR2024	Death	Definitely irrelevant	death
1006-0179	Placebo	04NOV2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
1006-0180	FYTF-919	02NOV2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
		06NOV2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
		06NOV2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
1006-0181	FYTF-919	02NOV2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0183	FYTF-919	08NOV2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
1006-0185	Placebo	14NOV2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
		06NOV2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0186	Placebo	07NOV2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0190	Placebo	22NOV2023	Liver failure	probably not relevant	Recovered/Resolved
		30NOV2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1006-0191	FYTF-919	14NOV2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0192	Placebo	17NOV2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0193	FYTF-919	14NOV2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0194	FYTF-919	14NOV2023	Pneumonia	Definitely irrelevant	death
		25NOV2023	Death	Definitely irrelevant	death
1006-0199	Placebo	22NOV2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0201	Placebo	04DEC2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
		16JAN2024	Death	Definitely irrelevant	death
1006-0202	FYTF-919	05DEC2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1006-0203	Placebo	06DEC2023	Pneumonia	Definitely irrelevant	death
		14DEC2023	Brain herniation	Definitely irrelevant	death
		14DEC2023	Death	probably not relevant	death
1007-0003	Placebo	08DEC2021	Pneumonia	Definitely irrelevant	Recovered/Resolved
1007-0009	Placebo	30JAN2022	Hydrocephalus	Definitely irrelevant	Recovered/resolved with sequelae
		22FEB2022	Cerebellar infarction	Unable to determine	Recovered/resolved with sequelae
1007-0012	Placebo	03JUN2022	Death	Definitely irrelevant	death
1007-0013	Placebo	20FEB2022	Uremia	Definitely irrelevant	Recovered/resolved with sequelae
1007-0016	FYTF-919	14MAR2022	Intracerebral hemorrhage	Definitely irrelevant	death
		02MAR2022	Pneumonia	Definitely irrelevant	death
		07APR2022	Death	Definitely irrelevant	death
		03APR2022	Brain herniation	Definitely irrelevant	death
		03APR2022	Intracranial infection	Definitely irrelevant	death
1007-0017	FYTF-919	07MAR2022	Death	Definitely irrelevant	death
		04MAR2022	Atrial fibrillation	Definitely irrelevant	death
		04MAR2022	Septicemia	Definitely irrelevant	death
1007-0027	Placebo	04JUL2022	Cardiac arrest	Definitely irrelevant	Recovered/resolved with sequelae
1007-0032	Placebo	02SEP2022	Acute upper gastrointestinal bleeding	Definitely irrelevant	Recovered/Resolved
1007-0036	FYTF-919	01JAN2023	Death	Definitely irrelevant	death
		09NOV2022	Pneumonia	Definitely irrelevant	death

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1007-0051	FYTF-919	26APR2023	Acute upper gastrointestinal bleeding	probably not relevant	Recovered/resolved with sequelae
1007-0060	Placebo	18AUG2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1007-0063	FYTF-919	05SEP2023	Death	Definitely irrelevant	death
		25AUG2023	Brain herniation	Definitely irrelevant	death
		31AUG2023	Hydrocephalus	Definitely irrelevant	death
1007-0070	FYTF-919	06FEB2024	Intracerebral hemorrhage	Definitely irrelevant	death
1007-0075	Placebo	08DEC2023	Pneumonia	Definitely irrelevant	death
		05DEC2023	Intracranial infection	Definitely irrelevant	death
1009-0001	FYTF-919	30JAN2022	Respiratory acidosis	Definitely irrelevant	death
		30JAN2022	Hypoalbuminemia	Definitely irrelevant	death
		29JAN2022	Pneumonia	Definitely irrelevant	death
		01FEB2022	Venous thrombosis limb	Definitely irrelevant	death
1009-0003	Placebo	15APR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		14APR2022	Upper gastrointestinal bleeding	probably not relevant	Recovered/Resolved
		27APR2022	Sepsis	Definitely irrelevant	Recovered/Resolved
1009-0008	Placebo	11AUG2022	Stress ulcer bleeding	Definitely irrelevant	Recovered/Resolved
		15AUG2022	Hepatic function abnormal	Definitely irrelevant	death
		16DEC2022	Death	Definitely irrelevant	death
1009-0013	Placebo	14NOV2022	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
		15NOV2022	Thrombocytopenia	Definitely irrelevant	Recovered/Resolved
1009-0014	FYTF-919	14NOV2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1009-0023	Placebo	24DEC2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1009-0024	Placebo	10JAN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		11JAN2023	Chronic renal failure acute exacerbation?	Possibly related	Recovered/resolved with sequelae
		11JAN2023	Hypoxemia	Definitely irrelevant	Recovered/Resolved
1009-0025	FYTF-919	27JAN2023	Acute renal insufficiency	Definitely irrelevant	Recovered/Resolved
1009-0035	FYTF-919	26MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1009-0038	FYTF-919	03JUL2023	Electrolyte imbalance	Definitely irrelevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1009-0039	Placebo	30JUN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		16JUL2023	Supraventricular tachycardia	Definitely irrelevant	Recovered/Resolved
1009-0040	FYTF-919	15AUG2023	Urinary tract infection	Definitely irrelevant	Recovered/Resolved
1009-0041	Placebo	04SEP2023	Gastrointestinal bleeding	probably not relevant	Recovered/Resolved
		15NOV2023	Death	Definitely irrelevant	death
1009-0042	FYTF-919	01OCT2023	Bacteremia	Definitely irrelevant	Recovered/resolved with sequelae
1009-0044	Placebo	15NOV2023	Intracerebral hemorrhage	Definitely irrelevant	Recovered/resolved with sequelae
		16NOV2023	Upper gastrointestinal bleeding	Definitely irrelevant	Recovered/Resolved
1009-0046	Placebo	01DEC2023	Hepatic function abnormal	Definitely irrelevant	Recovered/Resolved
1009-0047	FYTF-919	20DEC2023	Hepatic function abnormal	Definitely irrelevant	death
1009-0049	FYTF-919	03DEC2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1009-0051	Placebo	05DEC2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
		05DEC2023	Venous thrombosis limb	Definitely irrelevant	Recovered/resolved with sequelae
1009-0052	Placebo	11DEC2023	Death	Definitely irrelevant	death
1010-0001	Placebo	05APR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1010-0003	Placebo	19MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		26MAR2023	Sepsis	Definitely irrelevant	Recovered/Resolved
1010-0005	FYTF-919	14APR2023	Stroke-associated pneumonia	Definitely irrelevant	Recovered/Resolved
		12APR2023	Upper gastrointestinal bleeding	probably not relevant	Recovered/Resolved
1010-0014	FYTF-919	17AUG2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		17AUG2023	Upper gastrointestinal bleeding	probably not relevant	Recovered/Resolved
1010-0021	FYTF-919	05SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1010-0025	Placebo	24SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1010-0036	Placebo	01NOV2023	Stroke-associated pneumonia	Definitely irrelevant	death
		19DEC2023	Death	Definitely irrelevant	death
1010-0037	Placebo	01NOV2023	Stroke-associated pneumonia	Definitely irrelevant	Recovered/Resolved
1010-0039	FYTF-919	28NOV2023	Electrolyte imbalance	Definitely irrelevant	Recovered/Resolved
		10DEC2023	Anemia	Possibly related	Recovered/resolved with sequelae
		01DEC2023	Hepatic function abnormal	Definitely irrelevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1011-0003	FYTF-919	01DEC2021	Pneumonia	Definitely irrelevant	death
		10DEC2021	Death	Definitely irrelevant	death
		02DEC2021	Anemia	Definitely irrelevant	death
1011-0004	FYTF-919	27DEC2021	Acute upper gastrointestinal bleeding	Definitely irrelevant	death
		04FEB2022	Death	Definitely irrelevant	death
1011-0005	FYTF-919	16DEC2021	Gastrointestinal bleeding	probably not relevant	Recovered/Resolved
1011-0006	Placebo	19DEC2021	Pneumonia	Definitely irrelevant	Recovered/Resolved
1011-0007	Placebo	27DEC2021	Pneumonia	Definitely irrelevant	Recovered/Resolved
1011-0010	Placebo	08FEB2022	Death	Unable to determine	death
1011-0014	FYTF-919	14FEB2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		18FEB2022	Gastrointestinal bleeding	Possibly related	Recovered/Resolved
		18FEB2022	Diarrhea	Possibly related	Recovered/Resolved
1011-0017	Placebo	27MAR2022	Death	Definitely irrelevant	death
1011-0021	FYTF-919	24APR2022	Hemoptysis	Definitely irrelevant	death
		19APR2022	Pneumonia	Definitely irrelevant	death
		28APR2022	Anemia	Definitely irrelevant	death
1011-0030	FYTF-919	25SEP2022	Hypoalbuminemia	Definitely irrelevant	Recovered/Resolved
		25SEP2022	Malnutrition	Definitely irrelevant	Recovered/Resolved
1011-0032	FYTF-919	15OCT2022	Pneumonia	Definitely irrelevant	death
		16OCT2022	Gastrointestinal bleeding	Definitely irrelevant	death
		17OCT2022	Death	Definitely irrelevant	death
1011-0033	Placebo	17OCT2022	Intracranial infection	Definitely irrelevant	death
		19OCT2022	Gastrointestinal bleeding	Definitely irrelevant	death
		11OCT2022	Pneumonia	Definitely irrelevant	death
		25OCT2022	Death	Definitely irrelevant	death
1011-0035	FYTF-919	17OCT2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1011-0036	FYTF-919	21NOV2022	Upper gastrointestinal bleeding	probably not relevant	Recovered/Resolved
		05DEC2022	Septic shock	Definitely irrelevant	death
		05DEC2022	Anemia	probably not relevant	death

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
		17NOV2022	Pneumonia	Definitely irrelevant	death
1011-0037	FYTF-919	20NOV2022	Upper gastrointestinal bleeding	Possibly related	Recovered/Resolved
		22NOV2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1011-0040	Placebo	10APR2023	Death	Definitely irrelevant	death
1011-0042	Placebo	17DEC2022	Death	Definitely irrelevant	death
1011-0043	FYTF-919	21DEC2022	Respiratory failure	Definitely irrelevant	death
		15DEC2022	Pneumonia	Definitely irrelevant	death
		18DEC2022	Obstructive hydrocephalus	Definitely irrelevant	death
		24DEC2022	Death	Definitely irrelevant	death
1011-0046	Placebo	13FEB2023	Pneumonia	Definitely irrelevant	death
		10FEB2023	Symptomatic epilepsy	Definitely irrelevant	death
		12FEB2023	Respiratory failure type 2	Definitely irrelevant	death
1011-0050	FYTF-919	06MAR2023	Brain herniation	Definitely irrelevant	death
		06MAR2023	Intracerebral haemorrhage	Definitely irrelevant	death
1011-0054	Placebo	30MAR2023	Intracerebral haemorrhage	Definitely irrelevant	Recovered/Resolved
1011-0056	Placebo	14APR2023	Intracerebral haemorrhage	Definitely irrelevant	death
		18MAY2023	Death	Definitely irrelevant	death
1011-0060	FYTF-919	01MAY2023	Intracerebral haemorrhage	Definitely irrelevant	Recovered/Resolved
1011-0063	FYTF-919	11MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1011-0068	FYTF-919	22JUN2023	Aspiration pneumonia	Definitely irrelevant	death
		07OCT2023	Sepsis	Definitely irrelevant	Recovered/Resolved
1011-0070	FYTF-919	26JUL2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1011-0072	Placebo	21AUG2023	Symptomatic epilepsy	Definitely irrelevant	Recovered/Resolved
1011-0073	Placebo	23AUG2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1011-0077	Placebo	14SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1011-0079	Placebo	08OCT2023	Acute upper gastrointestinal bleeding	Definitely irrelevant	Recovered/Resolved
		28SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1011-0080	FYTF-919		Death	Definitely irrelevant	death
1011-0081	FYTF-919	21OCT2023	Intracerebral haemorrhage	Definitely irrelevant	death

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
		13OCT2023	Pneumonia	Definitely irrelevant	death
		23OCT2023	Death	Definitely irrelevant	death
1011-0084	FYTF-919	26OCT2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		02NOV2023	Gastrointestinal bleeding	probably not relevant	Recovered/Resolved
		02NOV2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
		03NOV2023	Intracranial haemorrhage	Definitely irrelevant	Recovered/resolved with sequelae
1011-0087	Placebo	06NOV2023	Anaemia	Possibly related	Recovered/Resolved
1011-0088	FYTF-919	06NOV2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1011-0094	Placebo	26DEC2023	Pneumonia	Definitely irrelevant	death
		24DEC2023	Anemia	Definitely irrelevant	death
		29DEC2023	Death	Definitely irrelevant	death
1012-0001	FYTF-919	27JAN2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1012-0002	Placebo	28JAN2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1012-0003	FYTF-919	09FEB2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1012-0004	FYTF-919	26FEB2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1012-0005	Placebo	01MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1012-0007	Placebo	12MAR2022	Death	Definitely irrelevant	death
		08MAR2022	Pneumonia	Definitely irrelevant	death
1012-0008	Placebo	30MAR2022	Haematoma expansion	probably not relevant	Recovered/resolved with sequelae
1012-0009	FYTF-919	19AUG2022	Haematoma expansion	Definitely irrelevant	death
		19AUG2022	Haematoma expansion	probably not relevant	death
		19AUG2022	Pneumonia	Definitely irrelevant	death
1012-0010	Placebo	23AUG2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		08NOV2022	Respiratory failure	Definitely irrelevant	Recovered/Resolved
		08NOV2022	Thrombocytopenia	Definitely irrelevant	Recovered/Resolved
1012-0011	Placebo	07SEP2022	Death	Definitely irrelevant	death
1012-0013	FYTF-919	09SEP2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1012-0014	Placebo	09SEP2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		30SEP2022	Acute respiratory distress syndrome	Definitely irrelevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
		12OCT2022	Respiratory failure	Definitely irrelevant	Recovered/Resolved
1012-0015	Placebo	23OCT2022	Acute respiratory distress syndrome	probably not relevant	Recovered/Resolved
		13OCT2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		02JAN2023	Death	Definitely irrelevant	death
1012-0019	Placebo	11FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1012-0021	FYTF-919	23MAR2023	Pneumonia	Definitely irrelevant	death
		10APR2023	Anemia	Definitely irrelevant	death
		04APR2023	Respiratory failure	Definitely irrelevant	death
		06APR2023	Pleural effusion	Definitely irrelevant	death
		12APR2023	Malnutrition	Definitely irrelevant	death
		04MAY2023	Multiple organ failure	Definitely irrelevant	death
1012-0023	FYTF-919	28MAR2023	Pneumonia	Definitely irrelevant	death
		03APR2023	Acute subdural haematoma	Definitely irrelevant	death
		08APR2023	Death	Definitely irrelevant	death
1012-0024	Placebo	11APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1012-0025	Placebo	11APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		21APR2023	Central respiratory depression	Definitely irrelevant	Recovered/Resolved
		23APR2023	Central respiratory depression	Definitely irrelevant	Recovered/Resolved
1012-0026	Placebo	28APR2023	Haematoma expansion	Definitely irrelevant	Recovered/Resolved
		28APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		01MAY2023	Thrombocytopenia	Definitely irrelevant	Recovered/Resolved
		01MAY2023	Anaemia	Definitely irrelevant	Recovered/Resolved
		03MAY2023	Anaemia	Definitely irrelevant	Recovered/Resolved
		02MAY2023	Respiratory failure	probably not relevant	Recovered/Resolved
1012-0028	Placebo	07MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1012-0029	Placebo	05JUN2023	Death	Definitely irrelevant	death
		18MAY2023	Pneumonia	Definitely irrelevant	death
1012-0030	FYTF-919	24MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		26MAY2023	Metabolic alkalosis	Definitely irrelevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1012-0031	FYTF-919	06JUN2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
		08JUN2023	Multiple organ failure	Definitely irrelevant	Recovered/Resolved
		08JUN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		07JUN2023	Respiratory failure	Definitely irrelevant	Recovered/Resolved
		06JUN2023	Bacteraemia	Definitely irrelevant	Recovered/Resolved
1012-0038	Placebo	04JUL2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		28SEP2023	Death	Definitely irrelevant	death
		03JUL2023	Difficulty breathing	Definitely irrelevant	Recovered/Resolved
		09JUL2023	Pleural effusion	Definitely irrelevant	death
		20JUL2023	Gastrointestinal bleeding	probably not relevant	death
		20JUL2023	Malnutrition	Definitely irrelevant	death
1012-0039	FYTF-919	11JUL2023	Pneumonia	probably not relevant	Recovered/Resolved
1012-0041	Placebo	04AUG2023	Death	probably not relevant	death
		02AUG2023	Pneumonia	Definitely irrelevant	death
1012-0042	FYTF-919	11AUG2023	Death	Unable to determine	death
		11AUG2023	Respiratory failure	Definitely irrelevant	Recovered/Resolved
		11AUG2023	Hyponatraemia	probably not relevant	death
1012-0043	Placebo	03SEP2023	Respiratory failure	probably not relevant	death
		30AUG2023	Pneumonia	Definitely irrelevant	death
1012-0044	Placebo	03SEP2023	Respiratory failure	probably not relevant	Recovered/Resolved
		31AUG2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1012-0045	Placebo	14OCT2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1013-0001	FYTF-919		Death	Definitely irrelevant	death
1013-0004	Placebo	07MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1013-0006	FYTF-919	13JUL2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1013-0007	Placebo	20NOV2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		22NOV2022	Intracranial infection	Definitely irrelevant	Recovered/Resolved
1013-0008	Placebo	28DEC2022	Brain herniation	Definitely irrelevant	death
		28DEC2022	Respiratory failure	Definitely irrelevant	death

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
		25DEC2022	Pneumonia	Definitely irrelevant	death
1013-0009	FYTF-919	20JAN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1013-0010	Placebo	20JAN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1013-0020	Placebo	23AUG2023	Intracerebral haemorrhage	Definitely irrelevant	Recovered/resolved with sequelae
1013-0024	Placebo	11NOV2023	Death	Definitely irrelevant	death
		07NOV2023	Obstructive hydrocephalus	Definitely irrelevant	death
1014-0004	FYTF-919	16MAR2023	Septic shock	Definitely irrelevant	death
		09MAR2023	Fever	Definitely irrelevant	death
		09MAR2023	Acute renal insufficiency	Definitely irrelevant	death
		09MAR2023	Stroke-associated pneumonia	Definitely irrelevant	death
1014-0008	FYTF-919		Death	Definitely irrelevant	death
1014-0009	FYTF-919	04APR2023	Death	Definitely irrelevant	death
		03APR2023	Stroke-associated pneumonia	Definitely irrelevant	death
1014-0011	Placebo	28APR2023	Multiple organ failure	Definitely irrelevant	death
		30APR2023	Pneumonia	Definitely irrelevant	death
		09MAY2023	Venous thrombosis deep limb	Definitely irrelevant	death
1014-0012	FYTF-919	29APR2023	Haematoma expansion	probably not relevant	death
1014-0015	Placebo		Death	Definitely irrelevant	death
1014-0016	Placebo	19MAY2023	Death	Definitely irrelevant	death
1014-0017	Placebo	08MAY2023	Stroke-associated pneumonia	Definitely irrelevant	death
1014-0018	FYTF-919	14MAY2023	Pneumonia	Definitely irrelevant	death
1014-0019	FYTF-919	15JUN2023	Respiratory failure	Definitely irrelevant	death
1014-0020	Placebo	08NOV2023	Pneumonia	Definitely irrelevant	death
1015-0006	FYTF-919	18MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		18MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1015-0008	Placebo	20MAR2023	Haematoma expansion	probably not relevant	Recovered/Resolved
		21MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1015-0010	FYTF-919	29MAR2023	Liver damage	Definitely irrelevant	Recovered/Resolved
1015-0011	Placebo	02APR2023	Anaphylactic shock	Definitely irrelevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1015-0012	Placebo	01APR2023	Pneumonia	Definitely irrelevant	death
		13APR2023	Death	Definitely irrelevant	death
		03APR2023	Hepatic function abnormal	probably not relevant	Recovered/resolved with sequelae
1015-0013	Placebo	01APR2023	Pneumonia	Definitely irrelevant	death
		19APR2023	Ischaemic stroke	Definitely irrelevant	death
		21APR2023	Death	Definitely irrelevant	death
1015-0025	FYTF-919	26MAY2023	Death	Definitely irrelevant	death
1015-0027	Placebo	07JUN2023	Death	Definitely irrelevant	death
1015-0035	Placebo	12JUN2023	Bacterial pneumonia	Definitely irrelevant	death
		18JUN2023	Acute renal failure	Definitely irrelevant	death
		03JUL2023	Death	Definitely irrelevant	death
1015-0036	Placebo	17JUN2023	Death	Definitely irrelevant	death
1015-0037	Placebo	06JUL2023	Obstructive hydrocephalus	Definitely irrelevant	Recovered/Resolved
1015-0038	FYTF-919	08JUL2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1015-0045	Placebo	01OCT2023	Death	Definitely irrelevant	death
1015-0046	FYTF-919	11OCT2023	Death	Definitely irrelevant	death
1015-0050	Placebo	16OCT2023	Death	Definitely irrelevant	death
1015-0052	FYTF-919	11NOV2023	Death	Definitely irrelevant	death
1016-0003	FYTF-919	11MAY2022	Gastroesophageal reflux	Definitely irrelevant	Recovered/Resolved
1016-0004	FYTF-919	19FEB2022	Pneumonia	Definitely irrelevant	death
		18APR2022	Death	Definitely irrelevant	death
1016-0005	Placebo	16MAR2022	Cognitive impairment	Definitely irrelevant	Recovered/resolved with sequelae
		25MAR2022	Gastrointestinal bleeding	probably not relevant	Recovered/Resolved
1016-0006	Placebo	25MAR2022	Fracture	Definitely irrelevant	Recovered/Resolved
1016-0008	Placebo	27APR2022	Pneumonia	Definitely irrelevant	death
		20MAY2022	Death	Definitely irrelevant	death
1016-0009	Placebo	28APR2022	Stroke-associated pneumonia	Definitely irrelevant	Recovered/Resolved
		06JUN2022	Diarrhea	Definitely irrelevant	Recovered/Resolved
1016-0010	Placebo	12JUL2022	Stroke-associated pneumonia	Definitely irrelevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
		05DEC2022	Death	Definitely irrelevant	death
1016-0011	FYTF-919	31JUL2022	Stroke-associated pneumonia	Definitely irrelevant	Recovered/Resolved
		17JAN2023	Pressure ulcer	Definitely irrelevant	Recovered/resolved with sequelae
1016-0013	FYTF-919	12SEP2022	Anxiety	Definitely irrelevant	Recovered/Resolved
1016-0014	FYTF-919	29SEP2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		29SEP2022	Brain herniation	Definitely irrelevant	Recovered/resolved with sequelae
1016-0015	Placebo	29SEP2022	Stroke-associated pneumonia	Definitely irrelevant	Recovered/Resolved
		02OCT2022	Gastrointestinal bleeding	Possibly related	Recovered/resolved with sequelae
		18DEC2022	Death	Definitely irrelevant	death
1016-0018	Placebo	22FEB2023	Hernia	Definitely irrelevant	Recovered/Resolved
1016-0019	FYTF-919	03NOV2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		03NOV2022	Consciousness impairment	Definitely irrelevant	Recovered/Resolved
		17NOV2022	Venous thrombosis deep	Definitely irrelevant	Recovered/resolved with sequelae
1016-0025	Placebo	20JAN2023	Hematoma expansion	Definitely irrelevant	Recovered/Resolved
		27JAN2023	Stroke-associated pneumonia	Definitely irrelevant	Recovered/Resolved
1016-0026	Placebo	10MAR2023	Venous thrombosis limb	Definitely irrelevant	Recovered/Resolved
1016-0028	Placebo	02JUN2023	Heart failure	Definitely irrelevant	death
1016-0029	Placebo	05JUN2023	Hydrocephalus	Definitely irrelevant	death
		05JUN2023	Stroke-associated pneumonia	Definitely irrelevant	death
1016-0033	FYTF-919	02OCT2023	Haematoma expansion	Definitely irrelevant	Recovered/Resolved
1016-0038	Placebo	04DEC2023	Venous thrombosis deep	Definitely irrelevant	Recovered/Resolved
1017-0003	FYTF-919	20DEC2021	Pneumonia	Definitely irrelevant	Recovered/Resolved
		16DEC2021	Hydrocephalus	Definitely irrelevant	Recovered/Resolved
1017-0004	Placebo	17DEC2021	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0005	FYTF-919	19DEC2021	Hypokalaemia	Definitely irrelevant	Recovered/Resolved
		17DEC2021	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0006	FYTF-919	19DEC2021	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0008	Placebo	18DEC2021	Haematoma expansion	Definitely irrelevant	death
		21DEC2021	Death	Definitely irrelevant	death

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1017-0010	FYTF-919	18DEC2021	Pneumonia	Definitely irrelevant	Recovered/Resolved
		21DEC2021	Hydrocephalus	Definitely irrelevant	Recovered/Resolved
1017-0012	Placebo	23DEC2021	Pneumonia	Definitely irrelevant	Recovered/Resolved
		30MAR2022	Death	Definitely irrelevant	death
1017-0015	FYTF-919	22DEC2021	Obstructive hydrocephalus	Definitely irrelevant	Recovered/Resolved
		27DEC2021	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0017	Placebo	27DEC2021	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0018	Placebo	24DEC2021	Intracerebral haemorrhage	Definitely irrelevant	death
		26DEC2021	Death	Definitely irrelevant	death
1017-0019	Placebo	26DEC2021	Obstructive hydrocephalus	Definitely irrelevant	Recovered/Resolved
1017-0023	FYTF-919	30DEC2021	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0025	FYTF-919	02JAN2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0026	FYTF-919	10JAN2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0027	Placebo	04JAN2021	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0030	Placebo	10JAN2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0037	Placebo	24JAN2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0039	FYTF-919	02FEB2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0040	Placebo	13FEB2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0042	FYTF-919	16FEB2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0043	Placebo	16FEB2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0045	FYTF-919	18FEB2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0051	Placebo	21FEB2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0054	Placebo	22FEB2022	Pneumonia	Definitely irrelevant	death
		24FEB2022	Death	Definitely irrelevant	death
1017-0057	FYTF-919	25FEB2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0062	Placebo	01MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0063	FYTF-919	01MAR2022	Death	Definitely irrelevant	death
		28FEB2022	Obstructive hydrocephalus	Definitely irrelevant	death
1017-0064	Placebo	27FEB2022	Pneumonia	Definitely irrelevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1017-0065	Placebo	28FEB2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0067	FYTF-919	01MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0068	FYTF-919	05MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0072	Placebo	04MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0078	Placebo	15APR2022	Gastrointestinal bleeding	Definitely irrelevant	death
		10MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0081	FYTF-919	12MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0083	Placebo	10MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0087	FYTF-919	12MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0090	FYTF-919	16MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0092	Placebo	15MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0093	FYTF-919	16MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0102	FYTF-919	24MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0105	Placebo	09MAY2022	Death	Definitely irrelevant	death
1017-0106	FYTF-919	28MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0107	Placebo	26MAR2022	Haematoma expansion	Definitely irrelevant	Recovered/Resolved
		27MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0108	FYTF-919	03APR2022	Intraventricular haemorrhage	Definitely irrelevant	death
1017-0110	FYTF-919	06APR2022	Haematoma expansion	Definitely related	Recovered/Resolved
		08APR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0111	Placebo	02JUL2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0112	FYTF-919	02JUL2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0120	FYTF-919	20JUL2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0122	Placebo	22JUL2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0123	FYTF-919	23JUL2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0124	Placebo	01OCT2022	Death	Definitely irrelevant	death
		26JUL2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		29JUL2022	Venous thrombosis limb	Definitely irrelevant	death
1017-0125	Placebo	26JUL2022	Pneumonia	Definitely irrelevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1017-0131	Placebo	05AUG2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0133	FYTF-919	12AUG2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0134	Placebo	17AUG2022	Pulmonary embolism	Definitely irrelevant	death
		26AUG2022	Death	Definitely irrelevant	death
1017-0141	Placebo	23AUG2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0142	Placebo	23AUG2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0144	FYTF-919	02SEP2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		02SEP2022	Haematoma expansion	Definitely irrelevant	Recovered/Resolved
1017-0146	FYTF-919	06SEP2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0148	FYTF-919	08SEP2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		07SEP2022	Haematoma expansion	Definitely irrelevant	Recovered/Resolved
1017-0153	Placebo	28SEP2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0157	Placebo	17OCT2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0160	Placebo	24OCT2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0161	Placebo	27OCT2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0163	Placebo	09NOV2022	Pneumonia	Definitely irrelevant	death
1017-0165	FYTF-919	16NOV2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		19NOV2022	Acute ischaemic stroke	Definitely irrelevant	Recovered/resolved with sequelae
1017-0166	FYTF-919	18NOV2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0171	Placebo	16DEC2022	Death	Definitely irrelevant	death
		25NOV2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0173	Placebo	25NOV2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0174	FYTF-919	26NOV2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0175	FYTF-919	21JAN2023	Death	Definitely irrelevant	death
		27NOV2022	Pneumonia	Definitely irrelevant	death
1017-0176	FYTF-919	01FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		30JAN2023	Haematoma expansion	Definitely irrelevant	Recovered/resolved with sequelae
1017-0178	FYTF-919	31JAN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0190	Placebo	09MAY2023	Death	Definitely irrelevant	death

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
		09FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0191	Placebo	07FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0192	FYTF-919	02APR2023	Death	Definitely irrelevant	death
1017-0197	Placebo	08FEB2023	Obstructive hydrocephalus	Definitely irrelevant	Recovered/Resolved
		14FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0201	FYTF-919	11FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0203	FYTF-919	12FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0206	Placebo	13FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0207	Placebo	13FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0208	Placebo	26FEB2023	Anemia	Definitely irrelevant	Recovered/resolved with sequelae
1017-0210	Placebo	15FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0217	Placebo	16FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0237	Placebo	01MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		26FEB2023	Obstructive hydrocephalus	Definitely irrelevant	Recovered/Resolved
1017-0239	Placebo	24FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		23FEB2023	Obstructive hydrocephalus	Definitely irrelevant	Recovered/Resolved
1017-0240	FYTF-919	25FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0248	Placebo	27FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0249	Placebo	27FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0256	Placebo	05MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0259	FYTF-919	15MAR2023	Stress ulcer bleeding	probably not relevant	Recovered/Resolved
		04MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0262	FYTF-919	03MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0264	Placebo	09MAR2023	Death	Definitely irrelevant	death
1017-0265	FYTF-919	08MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0266	FYTF-919	03MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0267	FYTF-919	04MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		31MAY2023	Death	Definitely irrelevant	death
1017-0271	Placebo	12APR2023	Cerebellar infarction	Definitely irrelevant	Recovered/resolved with sequelae

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
		25MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		06APR2023	Obstructive hydrocephalus	Definitely irrelevant	Recovered/Resolved
1017-0279	Placebo	29MAR2023	Stress ulcer bleeding	probably not relevant	Recovered/resolved with sequelae
1017-0285	Placebo	11APR2023	Ischaemic stroke	Definitely irrelevant	Recovered/resolved with sequelae
1017-0287	FYTF-919	29MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0288	Placebo	29MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0289	FYTF-919	03APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0290	FYTF-919	10APR2023	Gastrointestinal bleeding	probably not relevant	Recovered/Resolved
		04APR2023	Pneumonia	probably not relevant	Recovered/Resolved
1017-0291	FYTF-919	14APR2023	Death	Definitely irrelevant	death
		03APR2023	Obstructive hydrocephalus	Definitely related	Recovered/Resolved
1017-0292	Placebo	03APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0293	Placebo	06APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0302	FYTF-919	11APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0303	Placebo	14APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0304	Placebo	15APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0305	Placebo	01MAY2023	Epilepsy	Definitely irrelevant	Recovered/Resolved
		15APR2023	Haematoma expansion	Definitely irrelevant	Recovered/Resolved
		01MAY2023	Cerebral edema	probably not relevant	Recovered/Resolved
1017-0307	FYTF-919	17APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0311	FYTF-919	27APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		30APR2023	Subarachnoid haemorrhage	Definitely irrelevant	Recovered/Resolved
1017-0314	Placebo	06MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0315	FYTF-919	09MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0316	FYTF-919	20MAY2023	Death	Definitely irrelevant	death
1017-0318	Placebo	18MAY2023	Haematoma expansion	Definitely irrelevant	Recovered/Resolved
1017-0319	Placebo	21MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0321	FYTF-919	27MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0322	Placebo	27MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1017-0326	Placebo	04JUN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0327	Placebo	06JUN2023	Death	Definitely irrelevant	death
1017-0332	Placebo	18JUN2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1017-0333	FYTF-919	15JUN2023	Venous thrombosis limb	Definitely irrelevant	death
		08OCT2023	Ischaemic stroke	Definitely irrelevant	death
1017-0334	FYTF-919	12JUN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		15JUN2023	Venous thrombosis limb	Definitely irrelevant	Recovered/resolved with sequelae
1017-0340	Placebo	02JUL2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1017-0341	Placebo	04JUL2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0345	FYTF-919	16JUL2023	Intracranial haemorrhage	Definitely irrelevant	Recovered/resolved with sequelae
1017-0355	Placebo	20JAN2024	Death	Definitely irrelevant	death
		14AUG2023	Venous thrombosis limb	Definitely irrelevant	death
1017-0357	FYTF-919	12AUG2023	Pneumonia	Definitely irrelevant	death
		12AUG2023	Venous thrombosis limb	Definitely irrelevant	death
1017-0358	Placebo	11AUG2023	Pneumonia	Definitely irrelevant	death
		18AUG2023	Intracranial haemorrhage	Definitely irrelevant	death
1017-0361	FYTF-919	23AUG2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0364	Placebo	05SEP2023	Pulmonary embolism	Definitely irrelevant	Recovered/Resolved
		05SEP2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/Resolved
1017-0365	Placebo	03JAN2024	Death	Definitely irrelevant	death
1017-0366	Placebo	26AUG2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0367	Placebo	25AUG2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0369	FYTF-919	27AUG2023	Venous thrombosis deep limb	Definitely irrelevant	Recovered/resolved with sequelae
1017-0370	FYTF-919	05SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0371	FYTF-919	04SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0372	Placebo	07SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0373	FYTF-919	09SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0374	Placebo	13SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0375	Placebo	13SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1017-0376	FYTF-919	19SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0377	FYTF-919	22SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0378	FYTF-919	21SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0379	Placebo	23SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0380	Placebo	23SEP2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0391	FYTF-919	23DEC2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0392	FYTF-919	23DEC2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1017-0394	Placebo	26DEC2023	Intracranial haemorrhage	Definitely irrelevant	death
		26DEC2023	Brain herniation	Definitely irrelevant	death
1019-0001	Placebo	29MAR2022	Intracranial infection	probably not relevant	Recovered/Resolved
1019-0002	FYTF-919	31MAR2022	Death	Definitely irrelevant	death
1019-0003	Placebo	09APR2022	Intracranial infection	Definitely irrelevant	Recovered/Resolved
1019-0012	FYTF-919	05APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1019-0013	Placebo	11APR2023	Death	Definitely irrelevant	death
1019-0014	Placebo	15APR2023	Hypernatremia	Definitely irrelevant	death
		12APR2023	Hypokalaemia	Definitely irrelevant	Recovered/Resolved
		19APR2023	Death	Definitely irrelevant	death
1019-0017	Placebo	21APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1019-0019	FYTF-919	03MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1019-0020	Placebo		Death	Definitely irrelevant	death
1019-0023	Placebo	03JUN2023	Ventricular fibrillation	probably not relevant	death
		03JUN2023	Death	probably not relevant	death
		25MAY2023	Pneumonia	Definitely irrelevant	death
1019-0025	Placebo	23MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1019-0026	FYTF-919	31MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1019-0029	FYTF-919	30MAY2023	Haematoma expansion	Definitely irrelevant	death
		01JUN2023	Respiratory failure	probably not relevant	death
		01JUN2023	Death	probably not relevant	death
1019-0031	Placebo	13DEC2023	Death	Definitely irrelevant	death

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1019-0040	FYTF-919	03NOV2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1019-0041	Placebo	07NOV2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1019-0042	Placebo	08NOV2023	Death	Definitely irrelevant	death
1019-0043	FYTF-919	24NOV2023	Death	Definitely irrelevant	death
1019-0045	FYTF-919	08JAN2024	Death	Definitely irrelevant	death
1019-0046	Placebo	24JAN2024	Death	Definitely irrelevant	death
1019-0052	Placebo	11FEB2024	Death	Definitely irrelevant	death
		15DEC2023	Intracerebral haemorrhage	Definitely irrelevant	death
1019-0054	FYTF-919	13JAN2024	Acute ischaemic stroke	Definitely irrelevant	Recovered/resolved with sequelae
1019-0058	Placebo	15DEC2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1019-0060	FYTF-919	17DEC2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0002	FYTF-919	04JAN2022	Intracerebral haemorrhage	probably not relevant	Recovered/Resolved
1020-0003	Placebo	14JAN2022	Pneumonia	probably not relevant	Recovered/Resolved
1020-0006	Placebo	17FEB2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0007	FYTF-919	01MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0008	Placebo	09MAR2022	Pneumonia	Definitely irrelevant	death
1020-0009	Placebo	11MAR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0010	FYTF-919	15MAR2022	Death	Definitely irrelevant	death
1020-0014	FYTF-919	27MAR2022	Death	Definitely related	death
1020-0015	Placebo	27APR2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
		03MAY2022	Grand mal epilepsy	Definitely irrelevant	Recovered/Resolved
1020-0017	FYTF-919	04MAY2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0022	FYTF-919	09AUG2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0023	FYTF-919	06AUG2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0024	Placebo	05AUG2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0027	Placebo	27OCT2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0028	Placebo	04NOV2022	Respiratory failure type 1	Definitely irrelevant	Recovered/Resolved
		01NOV2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0030	FYTF-919	11NOV2022	Pneumonia	Definitely irrelevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1020-0034	FYTF-919	29DEC2022	Death	Definitely irrelevant	death
1020-0037	Placebo	02JAN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0038	FYTF-919	15JAN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0039	FYTF-919	12FEB2023	Heart failure	Definitely irrelevant	death
		12FEB2023	Pneumonia	Definitely irrelevant	death
1020-0042	FYTF-919	16FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0044	FYTF-919	24FEB2023	Kidney failure	Definitely irrelevant	death
		13MAR2023	Death	Definitely irrelevant	death
1020-0045	Placebo	09MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0047	Placebo	04APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0052	Placebo	28JUN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0053	FYTF-919	25JUL2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0054	Placebo	20AUG2023	Pneumonia	Definitely irrelevant	death
		05SEP2023	Death	Definitely irrelevant	death
1020-0056	Placebo	28OCT2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0059	FYTF-919	03DEC2023	Death	Definitely irrelevant	death
1020-0060	FYTF-919	09NOV2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
		08NOV2023	Hydrocephalus	Definitely irrelevant	death
		13NOV2023	Haematoma expansion	Definitely irrelevant	death
1020-0061	Placebo	09NOV2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0062	FYTF-919	10NOV2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0065	Placebo	08DEC2023	Death	Definitely irrelevant	death
1020-0066	FYTF-919	17NOV2023	Death	Definitely irrelevant	death
1020-0067	Placebo	20NOV2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0068	Placebo	25NOV2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1020-0070	Placebo	05DEC2023	Death	Definitely irrelevant	death
1023-0003	FYTF-919	31OCT2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1023-0004	FYTF-919	02JAN2023	Death	Definitely irrelevant	death
1023-0006	FYTF-919	26JAN2023	Respiratory failure	Definitely irrelevant	death

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1023-0007	Placebo	23JUL2023	Death	Definitely irrelevant	death
		04MAY2023	Intracerebral haemorrhage	Definitely irrelevant	Unknown
1023-0010	FYTF-919	21AUG2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1025-0001	Placebo	25MAR2023	Haematoma expansion	Definitely irrelevant	death
			Death	Definitely irrelevant	death
1025-0004	FYTF-919	08APR2023	Respiratory failure	Definitely irrelevant	death
		06APR2023	Central diabetes insipidus	probably not relevant	death
1026-0001	Placebo	08FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0002	FYTF-919	13FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0004	FYTF-919	26FEB2023	Anemia	Definitely irrelevant	Recovered/Resolved
		16FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0005	FYTF-919	20FEB2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0007	Placebo	01MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0008	Placebo	14MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0009	Placebo	03JUL2023	Death	Definitely irrelevant	death
1026-0010	FYTF-919	23MAR2023	Impaired liver function	probably not relevant	death
		22MAR2023	Anaemia	Definitely irrelevant	death
		23MAR2023	Pneumonia	Definitely irrelevant	death
		24MAR2023	stroke-related neurologic deficit	Definitely irrelevant	death
1026-0013	Placebo	02APR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		14APR2023	Impaired liver function	probably not relevant	Recovering/Resolving
1026-0014	FYTF-919	03APR2023	Pneumonia	probably not relevant	Recovered/Resolved
1026-0015	FYTF-919	03APR2023	Pneumonia	Definitely irrelevant	Unknown
1026-0016	Placebo	16APR2023	Pneumonia	probably not relevant	Recovered/Resolved
1026-0018	FYTF-919	19APR2023	Pneumonia	Definitely irrelevant	death
1026-0019	Placebo	13MAY2023	Impaired liver function	probably not relevant	Recovered/Resolved
		05MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0020	FYTF-919	07MAY2023	Hypocalcaemia	Definitely related	Recovered/Resolved
		08MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1026-0022	FYTF-919	20MAY2023	Pneumonia	probably not relevant	Recovered/Resolved
1026-0023	Placebo	03JUN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0024	Placebo	04JUN2023	Haematoma expansion	Definitely irrelevant	death
		02JUN2023	Pneumonia	probably not relevant	death
		15JUN2023	Stroke-related neurologic deficit	Definitely irrelevant	death
1026-0025	FYTF-919	05JUN2023	Hepatic function abnormal	Possibly related	Recovered/Resolved
1026-0026	FYTF-919	10JUN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0027	Placebo	15JUN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0029	Placebo	30JUN2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1026-0030	Placebo	30JUN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0032	Placebo	16JUL2023	Pneumonia	Definitely irrelevant	death
		17JUL2023	Hypoalbuminaemia	Definitely irrelevant	death
		17JUL2023	Anemia	Definitely irrelevant	death
1026-0033	Placebo	17JUL2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		22JUL2023	Liver damage	probably not relevant	Recovered/resolved with sequelae
1026-0034	Placebo	17JUL2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0035	FYTF-919	18JUL2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0036	FYTF-919	20JUL2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
		23JUL2023	Impaired liver function	probably not relevant	Recovered/Resolved
		03NOV2023	Death	Definitely irrelevant	death
		20JUL2023	Intracerebral haemorrhage	Definitely irrelevant	Recovered/Resolved
1026-0037	Placebo	02AUG2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0038	FYTF-919	28JUL2023	Pneumonia	probably not relevant	Recovered/Resolved
1026-0040	Placebo	03AUG2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0041	Placebo	12AUG2023	Pneumonia	Possibly related	Recovered/Resolved
		14AUG2023	Hypokalemia	Definitely irrelevant	Recovered/Resolved
1026-0042	FYTF-919	13AUG2023	Aspiration pneumonia	Definitely irrelevant	death
1026-0043	Placebo	14AUG2023	Intracerebral haemorrhage	Definitely irrelevant	death
		13AUG2023	Pneumonia	Definitely irrelevant	Unknown

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
		17AUG2023	Impaired liver function	probably not relevant	death
1026-0044	FYTF-919	18AUG2023	Pneumonia	probably not relevant	Recovered/Resolved
		18AUG2023	Respiratory failure type 2	probably not relevant	Recovered/Resolved
1026-0045	FYTF-919	18AUG2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0048	FYTF-919	31AUG2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1026-0050	FYTF-919	29AUG2023	Pneumonia	Definitely irrelevant	death
		29AUG2023	Acidosis	Definitely irrelevant	Recovered/Resolved
		29AUG2023	Hypocalcaemia	Definitely irrelevant	death
1028-0001	Placebo	02MAR2022	Intracranial infection	probably not relevant	death
		23MAR2022	Death	probably not relevant	death
		03MAR2022	Haematoma expansion	probably not relevant	death
		04MAR2022	Pneumonia	Definitely irrelevant	death
1028-0005	FYTF-919	30APR2022	Septic shock	probably not relevant	death
		21APR2022	Pneumonia	Definitely irrelevant	death
		01MAY2022	Death	Definitely irrelevant	death
1028-0006	Placebo	20JUL2022	Circulatory failure	probably not relevant	death
		16JUL2022	Intracranial infection	Definitely irrelevant	death
1028-0007	FYTF-919	18JUL2022	Intracranial infection	probably not relevant	Recovered/Resolved
		20JUL2022	Pneumonia	probably not relevant	Recovered/Resolved
1028-0008	Placebo	24JUL2022	Pneumonia	probably not relevant	Recovered/Resolved
		22JUL2022	Intracranial infection	probably not relevant	Recovered/Resolved
1028-0009	FYTF-919	09AUG2022	Respiratory failure	Definitely irrelevant	death
1028-0010	Placebo	25AUG2022	Pneumonia	probably not relevant	Recovered/Resolved
1028-0011	FYTF-919	18OCT2022	Venous thrombosis limb	Definitely irrelevant	Recovered/Resolved
		31OCT2022	Anemia	Definitely irrelevant	death
		19OCT2022	Pneumonia	Definitely irrelevant	death
1028-0012	Placebo	19NOV2022	Intracranial infection	Definitely irrelevant	Recovered/Resolved
		16NOV2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1028-0014	FYTF-919	16DEC2022	Venous thrombosis limb	probably not relevant	Recovered/Resolved

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
		06DEC2022	Pneumonia	Definitely irrelevant	Recovered/Resolved
1028-0016	Placebo	05JAN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1028-0017	FYTF-919	16JAN2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1028-0019	FYTF-919	21MAR2023	Pneumonia	Definitely irrelevant	death
		21MAR2023	Intracranial infection	Definitely irrelevant	death
1028-0020	FYTF-919	06APR2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
1028-0021	FYTF-919	06MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		28APR2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
1028-0022	Placebo	15MAY2023	Intracranial infection	Definitely irrelevant	Recovered/Resolved
1028-0024	Placebo	06DEC2023	Pneumonia	probably not relevant	Recovered/Resolved
		11DEC2023	Intracranial infection	probably not relevant	Recovered/Resolved
1029-0005	FYTF-919	27DEC2022	Pneumonia	probably not relevant	Recovered/Resolved
1029-0008	Placebo	07MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
1029-0009	FYTF-919	16MAR2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		16MAY2023	Death	Definitely irrelevant	death
1030-0002	Placebo	14DEC2022	Venous thrombosis limb	Definitely irrelevant	Recovered/Resolved
1030-0003	FYTF-919	05MAR2023	Septic shock	probably not relevant	death
		03MAR2023	Respiratory failure	probably not relevant	death
		04MAR2023	Atrial fibrillation	probably not relevant	Recovered/Resolved
1031-0004	FYTF-919	24JAN2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1031-0006	FYTF-919	26JAN2023	Bacterial pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
		23JUN2023	Death	Definitely irrelevant	death
1031-0013	FYTF-919	09FEB2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1031-0019	Placebo	07MAR2023	Gastrointestinal bleeding	probably not relevant	Recovered/resolved with sequelae
1031-0029	FYTF-919	04APR2023	Intracerebral haemorrhage	Definitely irrelevant	Recovered/resolved with sequelae
1031-0037	FYTF-919	22APR2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1031-0038	FYTF-919	23APR2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
		23APR2023	Impaired liver function	Definitely irrelevant	Recovered/Resolved
1031-0040	Placebo	30APR2023	Pneumonia	Definitely irrelevant	death

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
		02MAY2023	Acute respiratory failure	Definitely irrelevant	Recovered/Resolved
		10MAY2023	Atrial fibrillation	Definitely irrelevant	Recovered/Resolved
		07MAY2023	Impaired liver function	Definitely irrelevant	death
		30APR2023	Renal insufficiency	Definitely irrelevant	death
		12MAY2023	Ischemic stroke	Definitely irrelevant	death
1031-0041	FYTF-919	03MAY2023	Pneumonia	Definitely irrelevant	Recovered/Resolved
		17MAY2023	Impaired liver function	probably not relevant	Recovered/Resolved
1031-0043	Placebo	08MAY2023	Intracerebral haemorrhage	Definitely irrelevant	Recovered/resolved with sequelae
		10MAY2023	Anemia	Definitely irrelevant	Recovered/Resolved
		10MAY2023	Coagulation disorder	Definitely irrelevant	Recovered/Resolved
1031-0048	FYTF-919	20MAY2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1031-0050	Placebo	22MAY2023	Haematoma expansion	Definitely irrelevant	Recovered/resolved with sequelae
		24MAY2023	Hepatic function abnormal	Possibly related	Recovered/Resolved
1031-0051	FYTF-919	25MAY2023	Pneumonia	Definitely irrelevant	death
		22JUN2023	Death	Definitely irrelevant	death
1031-0052	Placebo	30MAY2023	Hematoma expansion	Definitely irrelevant	death
		03JUN2023	Death	Definitely irrelevant	death
		02JUN2023	Intracerebral haemorrhage	Definitely irrelevant	death
1031-0055	FYTF-919	03JUL2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1031-0058	FYTF-919	02SEP2023	Acute respiratory failure	Definitely irrelevant	Recovered/Resolved
		27AUG2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1031-0059	Placebo	26SEP2023	Communicating hydrocephalus	Definitely irrelevant	Recovered/resolved with sequelae
1031-0060	FYTF-919	17SEP2023	Pneumonia	Definitely irrelevant	death
		18SEP2023	Intracerebral haemorrhage	Definitely irrelevant	death
1031-0062	Placebo	06OCT2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1031-0063	Placebo	18OCT2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1031-0067	Placebo	14NOV2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
		10APR2024	New Intracerebral haemorrhage	Definitely irrelevant	Recovered/resolved with sequelae
1031-0068	FYTF-919	14NOV2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae

Subject ID	Treatment group	Onset date	AE term	Relationship with treatment	Outcome
1031-0071	Placebo	18NOV2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1031-0075	FYTF-919	30NOV2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1031-0076	FYTF-919	30NOV2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1031-0077	FYTF-919	07DEC2023	Pneumonia	Definitely irrelevant	Recovered/resolved with sequelae
1031-0079	FYTF-919	16DEC2023	Cardiac arrest?	Definitely irrelevant	Recovered/Resolved
		01MAY2024	Ischaemic stroke	Definitely irrelevant	Recovered/resolved with sequelae
1031-0082	FYTF-919	26DEC2023	Pneumonia	Definitely irrelevant	death
		08MAR2024	Death	Definitely irrelevant	death
1031-0083	FYTF-919	03JAN2024	Hepatic function abnormal	Definitely irrelevant	death
		11JAN2024	Death	Definitely irrelevant	death

18. Figures

Figure S1. Trial profile to Day 180

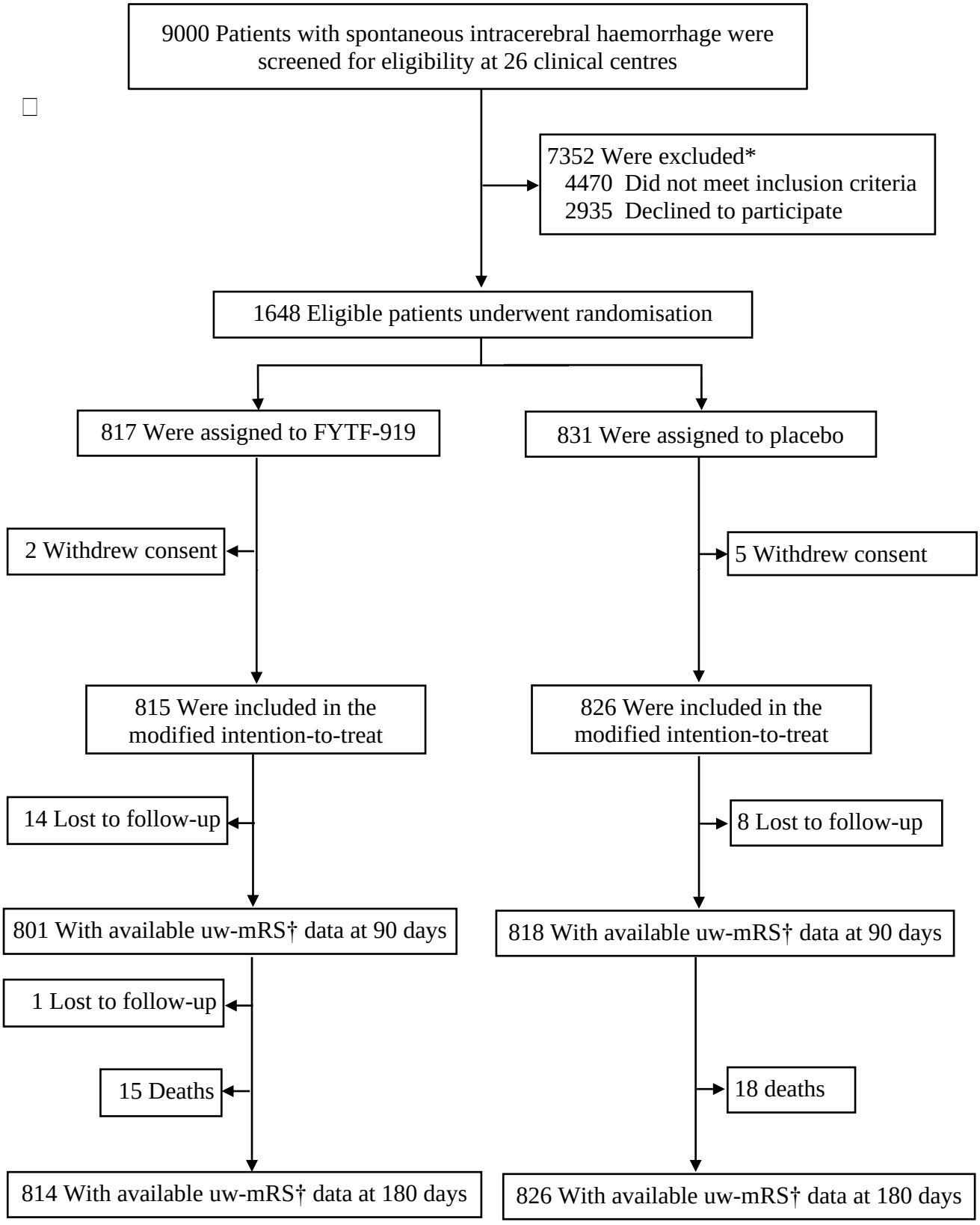
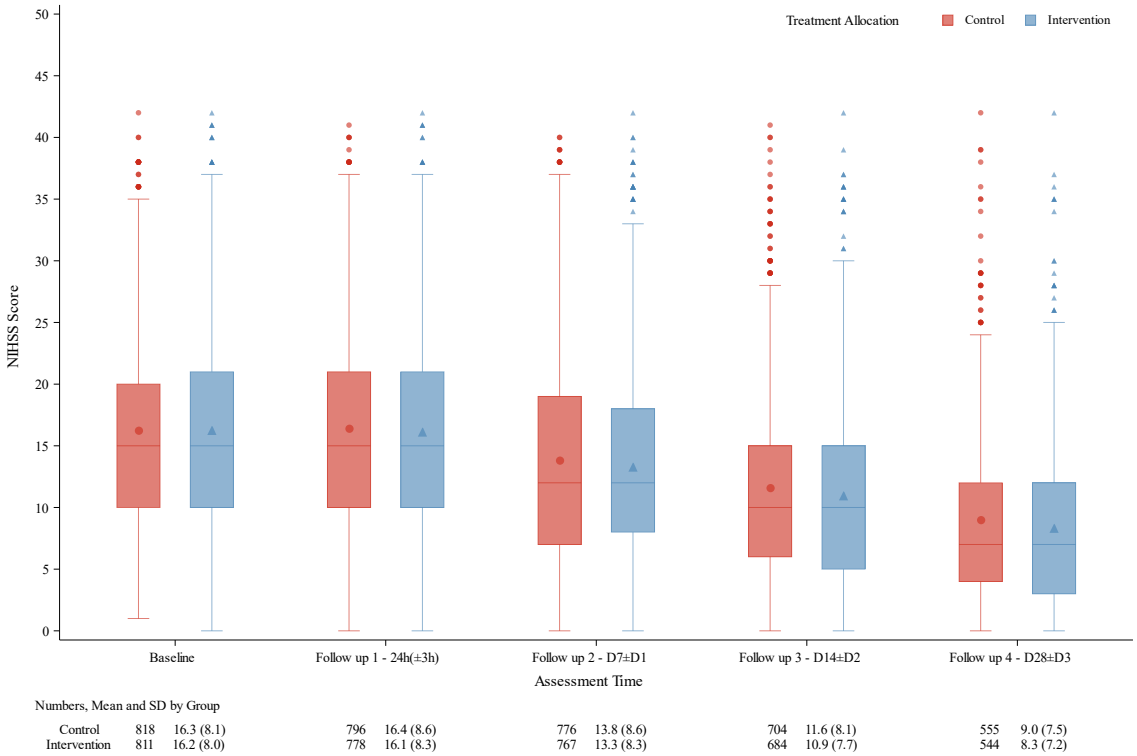


Figure S2. National Institutes of Health Stroke Scale score distribution over time



*

Figure S3. Analysis of the treatment effect across re-classification of subgroups at 90 days

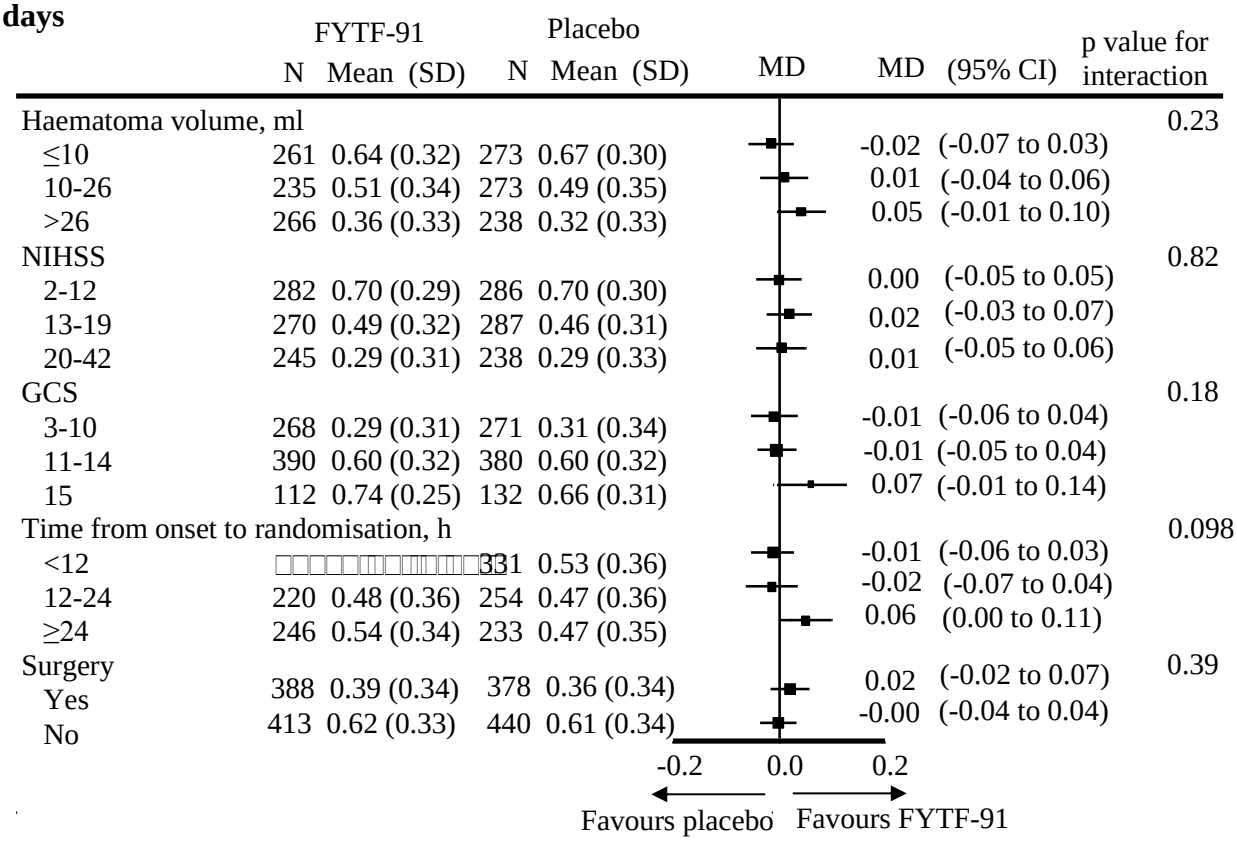


Figure S4. Analysis of the treatment effect across subgroups at 180 days

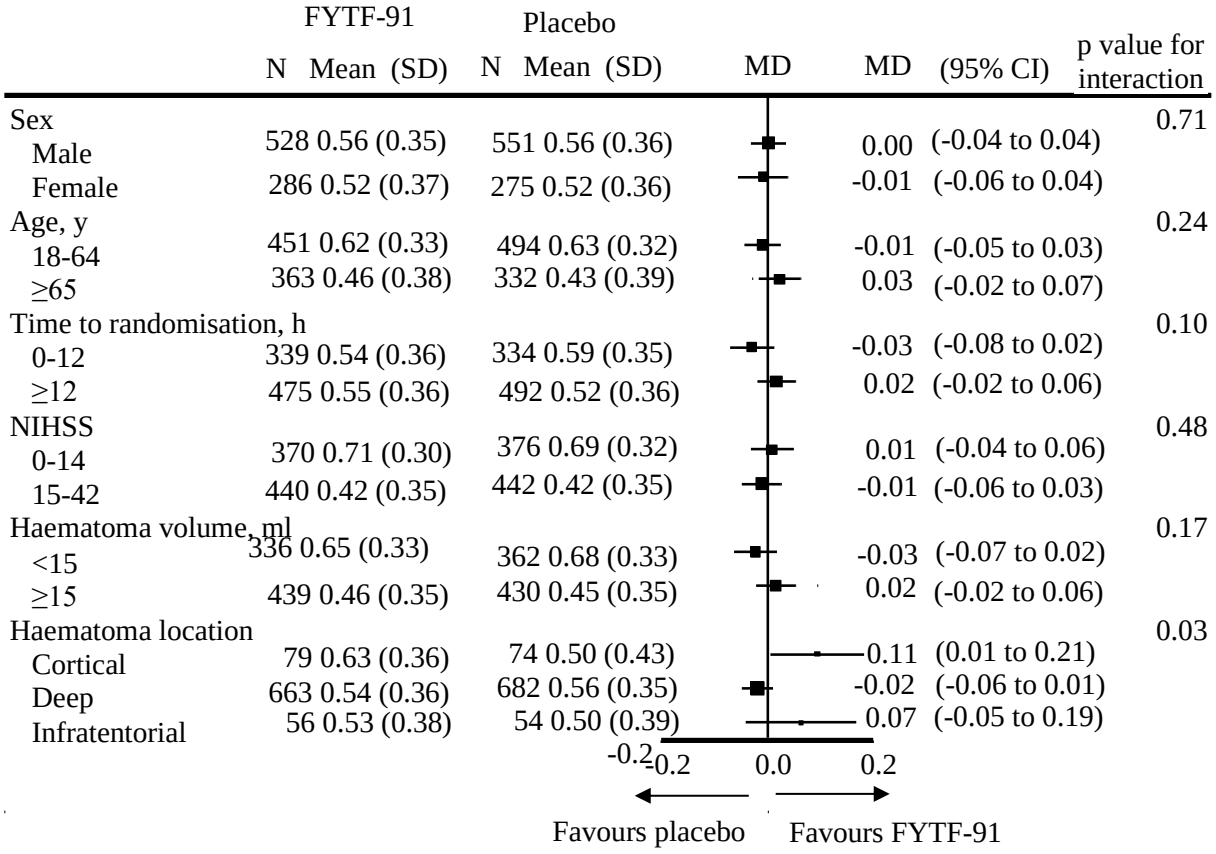
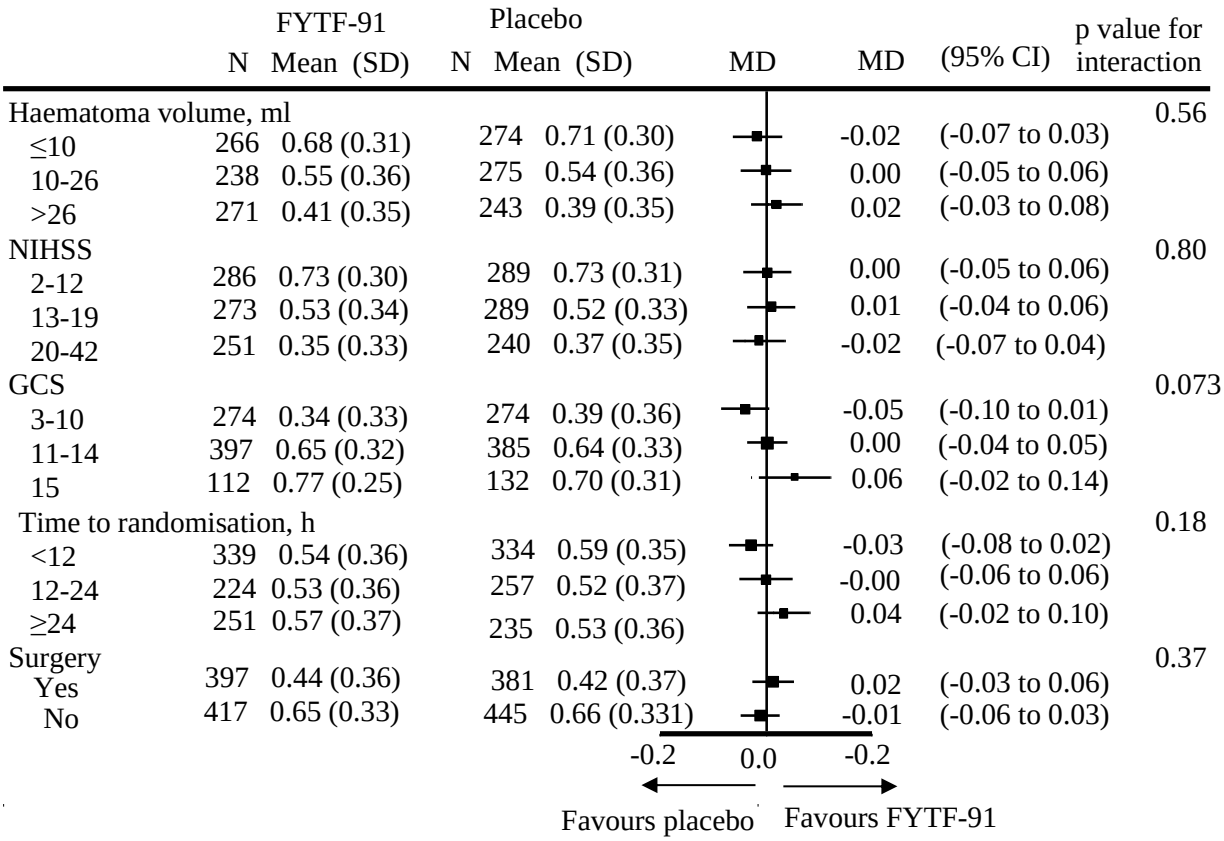


Figure S5. Analysis of the treatment effect across re-classification of subgroups at 180 days



Chinese herbal medicine (Zhongfeng Xingnao preparations) for spontaneous intracerebral hemorrhage: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Intracerebral hemorrhage (ICH) is a sub-type of fatal and poorly treatable stroke. Zhongfeng Xingnao (ZFXN) preparation, is a multi-herb prescription of Chinese herbal medicine, which was patented as a novel medicine, and manufactured as an oral solution for the clinical treatment of ICH. This systematic review was to assess the efficacy and safety of ZFXN for ICH .

Methods: To identify eligible RCTs on ZFXN for acute ICH, electronic databases, clinical trial registries and unpublished reports were searched up to March 2024. Literature screening, data extraction and risk of bias assessment were performed by two independent reviewers and validated by the third one. A pairwise meta-analysis was conducted followed by subgroup analyses and sensitivity analyses. The evidence quality was assessed by the GRADE approach.

Results: A total of nine RCTs were included to the review. Evidence of moderate quality suggested that in the participants with ICH, the adjunct use of ZFXN preparation to conventional medicine reduced mortality (RR: 0.54, 95%CI: 0.40 to 0.74, I^2=31%, n=6 RCTs, 1060 participants), improved 90-day activities of daily living per Barthel index (MD: 13.76, 95%CI: 11.22 to 16.30, I^2=33%, n=5 RCTs, 431 participants), and decreased the volume of cerebral hematoma (MD: -3.88 ml, 95%CI: -4.87 to -2.88, I^2=45%, n=4 RCTs, 694 participants). Though ZFXN presented add-one effect on improved neurological impairments per National Institute of Health stroke scale (MD: -2.37, 95%CI: -3.34 to -1.39, I^2=66%, n=6 RCTs, 994 participants), the evidence was low quality due to heterogeneity and risk of bias. Generally, ZFXN did not increase the risk of adverse events (RR: 1.08, 95%CI: 0.69, 1.69, I^2=53%, n=7 RCTs, 1079 participants), but the occurrence of diarrhea was markedly increased. The subgroup-analyses suggested that ICH participants with 20-35 ml hematoma volume at baseline and those with the therapeutic duration ≥ 28 days were likely to benefit most from ZFXN.

Conclusion: Clinical evidence of low-to-moderate quality suggested that adjunct ZFXN preparation was potentially effective and safe for acute ICH. However, a multi-site, larger sample, confirmatory RCT with improved methodological design and quality control was needed, before its comparative research with other proprietary Chinese medicine.

Registration: PROSPERO No. CRD42021247243.

Keywords: spontaneous intracerebral hemorrhage; Chinese herbal medicine; meta-analysis

Introduction

Intracerebral hemorrhage (ICH), caused by rupture of blood vessels in the brain, is one of the most fatal and poorly treatable subtypes of stroke, and it affects more than 3 million people annually worldwide.[1] It is a life-threatening and disabling event in which 13%-61% patients die within the first month of ictus, leaving less than 30% survivors achieving functional independence at 6-months.[2-3] For individuals with mild to moderate ICH, the strategy of lowering acute blood pressure aiming at limiting blood pressure variability and achieving a smooth, sustained blood pressure, is considered beneficial to functional outcomes and with strong recommendations in clinical practice guidelines.[4] Regarding the large or severe ICH, the evacuation of hematoma and surgical decompression are likely to reduce the mortality, but it was not associated with improved functional outcomes.[5] A recent international multi-site clinical trial suggests that the goal-directed care bundle of early physiological control including the intensive BP lowering, glycaemic control, and treatment of pyrexia, and the reversal of anticoagulation in the participants of ICH is associated with a reduced death at 6 months, but it has no apparent impacts on major disability in those survivors.[6] Though the rehabilitation and recovery are critical to better functional outcomes and quality of life after ICH of moderate severity,[4,7] the timing of implementing rehabilitation activities is conflicting as some study suggests that very early aggressive mobilization might cause a higher mortality.[8,9] In summary, there is no certain evidence on any single medication that has been shown to significantly improve mortality and neurological outcome after ICH, and an increase in the number of ICH clinical trials may provide continued hope for reducing its burden.[10]

Chinese herbal medicine (CHM) has long been applied in the treatment of stroke, and it continues to be widely used in modern China,[11,12] and accumulated clinical evidence suggests that CHM as an adjunct to conventional medications and rehabilitation provides additional benefits to the patients with stroke.[13] However, most high-quality clinical trials are for ischemic stroke,[14-16] and the CHM recommendations specific to ICH in clinical practice guidelines are mostly based on expert consensus and evidence of low quality.[17] Given the unmet demand for the research and discovery of new drugs for ICH, medical scientists attempt to assess the effect and safety of CHM for ICH, and a meta-analysis pooling 45 clinical trials showed that the add-one use of CHM to conventional treatments safely improved the dependency, neurological impairments, and volume of hematoma and perihematomal edema; however, it did not offer additional benefits to mortality.[18]

Zhongfeng Xingnao (ZFXN) preparation, a multi-herbal formula of CHM, developed from Dr. Shaohong Chen, the Master of Chinese Medicine entitled by Chinese national government, has been used in the treatments of ICH for more than 25 years. From the perspective of Traditional Chinese medicine (TCM) theory, Dr Chen believes that Qi deficiency is essential to the pathophysiological process of acute ICH, which is quiet different from the theory and clinical experience of other TCM practitioners.[19,20] ZFXN preparations are currently composed of four herbs, namely, *Ginseng (Radix Ginseng)*, *Chuanxiong (Rhizoma Ligustici Chuanxiong)*, *Sanqi (Radix Notoginseng)*, and *Dahuang (Radix et Rhizoma Rhei)*, which is patented as a novel treatment for cerebrovascular disease in 2005.[21] A review of laboratory experiments suggests that ZFXN preparations can be well penetrated to the blood brain barrier (BBB), and the whole formula presents the effect of anti-inflammations, anti-oxidants, the inhibition of excitatory toxicity, antiapoptosis, neuro-protection and maintaining the integrity of BBB.[22] To be specific, in a rat model of collagenase-VII-induced ICH, five-days treatment of ZFXN is able to improve the neurological deficits, the hematoma and perihematoma edema, which may be via the mechanism that ZFXN down-regulates expressions of CaMKII/NF-κB p65/NLRP3/GSDMD signaling axis-related protein around the hematoma area, and attenuates the inflammatory response by regulating the activation of NLRP3 inflammasome after ICH.[23] A study using the network pharmacology and molecular docking techniques suggests that ZFXN inhibits neuronal apoptosis and inflammatory response through PI3K/AKT/p53 pathway to protect the BBC, thereby slowing down microcirculatory impairment in cerebral hemorrhage, which is validated by the experiment conducted in ICH rat models.[24]

ZFXN preparation has been manufactured as an oral solution, and put into use in the Hospital of Chendu University of TCM for almost 17 years, which is approved and regulated by Sichuan Medical Products Administration (Batch number: Z20070623).[25] Over the decades, small-to-middle scale clinical trials on ZFXN preparations for ICH had been performed to assess its effect and safety, and to further explore the optimal timing of administration and best-fit subgroup population; however, a systematic review and meta-analysis pooling these studies was lacking. Therefore, we conducted this systematic review and meta-analysis on ZFXN for ICH to address these clinical questions, including

- Did ZFXN benefit the patients with acute ICH per critical outcomes?
- Did the add-one use of ZFXN to conventional treatment bring additional risks to the patients with acute ICH?
- Which was the best administration timing and therapeutic duration of ZFXN?

■□ What type of ICH patients would benefit best from the treatment of ZFXN?

Methods

The protocol of this systematic review was prospectively registered in PROSPERO (CRD42021247243),[26] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020.[27]

1. Eligibility Criteria

Studies met the following inclusion criteria were included to the systematic review.

Types of studies

Randomized controlled trials (RCTs) were eligible.

Participants

The participants were diagnosed as spontaneous ICH confirmed by imaging.

Interventions and controls

The experimental intervention was ZFXN preparations consisting of Ginseng (*Radix Ginseng*), Chuanxiong (*Rhizoma Ligustici Chuanxiong*), Sanqi (*Radix Notoginseng*), and Dahuang (*Radix et Rhizoma Rhei*), in the forms of traditional CHM decoction, and proprietary CHM, such as oral solution and granule. The control included no treatment, placebo, standard care, disease management (e.g.controlling blood pressure, glucose, and temperature, and the prevention from medical complications), and medical treatments (e.g. pharmacotherapy to decrease the intracranial pressure, or surgery). Studies examining either the independent or the add-one effect of ZFXN were included.

Outcome measurements

The primary outcomes were the mortality and neurological impairments such as National Institutes of Health Stroke Scale (NIHSS). The secondary outcomes included dependency assessed with modified Rankin Scale (mRS), and Barthel Index (BI), volume of hematoma, and perihematomal edema. The safety outcomes including general adverse events, and specific to ICH.

If the studies met one of the following criteria were excluded:

■□ ICH was certainly due to brain trauma, aneurysm, cerebrovascular malformation, tumor and inappropriate use of anti-coagulant or anti-platelet treatment;

■□ Other CHM regimens were used in the intervention groups;

■□ The basic care and treatment differed between the intervention and control group; and

■□ Duplicates.

2. Data sources and search strategies

We searched eight databases, including the Cochrane Library, PubMed, EMbase, Web of Science, Chinese National Knowledge Infrastructure (CNKI), WanFang database, VIP Chinese SciTech Periodical Database (VIP) and China Biological Medicine Database (CBM) from their inceptions until March 2024. We also searched studies completed yet unpublished in clinical trial registries including Chinese Clinical Trial Registry (ChiCTR) and ClinicalTrials.gov. In addition, we contacted the research and development team of ZFXN for detailed research reports and datasets of unpublished RCTs. The full search strategies are presented in Supplementary Table S1.

3. Study selection and data extraction

After removing duplicates, two reviewers independently screened the literature by reviewing the titles and abstracts, followed by reading the full texts to identify the relevant studies. The data were extracted in the manner of double entry. The data item included the author, publication year, study design, sample size, age, sex, diagnosis, time of onset (hour), hematoma volume (ml), and the details of interventions such as type of preparations, dosage, therapeutic duration, and outcome. Disagreements in the process of study selection and data extraction were settled through discussion or consultation with a third reviewer.

4. Risk of bias assessment and evidence quality

Two independent reviewers assessed the risk of bias (RoB) of included studies using the Cochrane RoB 2 tool.[28] Five domains including bias arising from the randomization process, bias due to deviations from intended interventions, due to missing outcome, bias in measurement of the outcome, and bias in selection of the reported result were evaluated using signaling questions. The RoB judgement for each domain was categorised as low risk of bias, some concerns, or high risk of bias. These levels of Rob were applicable to an overall RoB judgement. Any disagreement was resolved by discussion or consultation with a third reviewer. As different impacts of blinding on the objective outcomes from clinician/participants reporting outcomes existed, we assessed the domains related to blinding per type of outcome measures.

The evidence quality of critical outcomes based on the consensus of the review panel, was assessed by the approach of Grading of Recommendations Assessment, Development, and Evaluation (GRADE),[29] and the certainty of evidence body was graded as high, moderate, low, or very low by considering the risk of bias, inconsistency, indirectness, imprecision, and publication bias.

5. Data presentation and meta-analysis

Dichotomous outcomes were presented as the risk ratio (RR) with a 95% confidence interval (CI), while continuous outcomes were primarily presented with mean differences (MD). Heterogeneity was assessed by the Cochrane Q-statistic test with the I^2 value. A fixed effect model was applied in the meta-analysis when the I^2 was less than 50%; otherwise, a random effect model was used. Sensitivity analysis was performed by omitting each study in turn. To explore the heterogeneity and identify the effect in certain types of participants, subgroup-analyses were conducted in terms of age, sex, time of onset, disease severity such as NIHSS scores and hematoma volume during the baseline, the types, dose, therapeutic duration of intervention and the type of control. Publication bias was assessed by the funnel plots with Egger's test when the meta-analysis included more than 10 studies. The data were analyze using the Review Manager software 5.3 and STATA 14.0.

Results

1. Study identification

The literature search identified 4,874 relevant records, three records identified thorough Chinese clinical trial registry. After removing duplicates and literature screening, a total of 9 RCTs published were finally included in the systematic review.[30,31,32,33,34,35,36,37,38] The full process of literature screening is specified in Figure 1.

2. Characteristics of the included studies

Table 1 detailed the basic characteristics of included studies. The included studies were published in Chinese medical journals between 2003 and 2023. The sample size ranged from 38 to 547, with an average of 160. All the included studies were ransomised, paralelled, controlled trials, and six of them were implemented in multiple sites.[33,34,35,36,37,38] Both the research personnel and participants were blinded in two trials,[37,38] while one study blinded the outcome assessor.[38] The participants were aged 66.12 years, and the male accounted for 44.4% of the total sample. In terms of the ICH definition, though different versions of national diagnostic standards were endorsed, including version 1995 (n=3), version 2005 (n=4), and version 2 (n=2), all of them were confirmed by clinical signs and imaging. Almost all the studies recruited the participants with an onset of ICH with 72 hours except one study also included participants with a disease course between 72 hours and seven days. All the studies had basal ganglia area as the local lesions, of which, five studies also included participants with other lesions, including lobe, cerebellum, and brainstem.[30,34,35,36,38] Regarding the ICH severity, among those reporting the NIHSS scores during the baseline, four scored more than 15 points[33,34,35,38] and two scored 5-15 points[30,37]; while in terms of hematoma volume, the range was between 15 ml and 35ml, five studies with more than 20ml[30,32,35,36,38] and two with less than 20ml.[34,37] Nursing, management of blood pressure, glucose, temperature, treatment on the complications such as pepticulcer, cerebral hernia and lung infection were implemented in compliance with clinical guidelines for all the participants. The participants in one trial underwent surgery treatment.[38] Although all the ZFXN preparation included Ginseng (*Radix Ginseng*), Chuanxiong (*Rhizoma Ligustici Chuanxiong*), Sanqi (*Radix Notoginseng*), and Dahuang (*Radix et Rhizoma Rhei*), they differed in preparations, including oral solution (n=6 studies), traditional decoction (n=2 studies), and granule (n=1 study). Dehydrants were forbidden in two studies.[30,32] The placebo to mimic ZFXN preparations was applied in three studies.[35,37,38] As for the outcome measurements, mortality was endorsed in six studies, neurological functions was measured in eight studies, including NIHSS (n=6 studies), ESS

(n=1), and MESSS (n=2), dependency was assessed in six studies, including Barthel index for activities of daily living (n=6), modified Ranking scale for disability (n=2), and post-treatment hematoma volume was calculated in six studies. Almost all the studies monitor the safety except one study.[36]

3. Risk of bias

Bias arising from the randomization process

Three studies[35,37,38] was judged as low risk of bias arising from the randomization process because they full reported the methods to generate the random sequence (eg. computer software and central randomization system) and the concealment of sequence allocation (eg. opaque sealed envelopes and central allocation system) while bias in other studies[30,31,32,33,36] were considered as some concerns mainly because they did not concealed the allocation.

Bias due to deviations from intended interventions and bias in measurement of the outcome

For the bias due to deviations from intended interventions and bias in measurement of the outcome, we made the judgments per outcomes including clinician-reporting outcome (CRO) such as NIHSS and objective outcome such as mortality. A total of eight studies measure the objective outcomes, two of which were allocated with low risk in bias due to deviations from intended interventions as they were double-blinded RCTs and they treated the outcome data with appropriate statistical methods[35,37]; another two[35,37] were judged as some concern because they were open-labeled, but they used intention-to-treat (ITT) analysis for the data of objective outcomes. Other studies[30,31,32,38] were at high risk of bias due to deviations from intended interventions because all of them did not treat the outcome data properly. A total of eight studies measured CROs, two of which were judged as low risk in this domain, because they were double-blinded and used ITT analysis, while bias in other studies were considered as high risk because they did not analyse the outcome data appropriately[38] or lacking the procedure of blinding[30,31,34,33,36]. For eight studies assessing objective outcomes[30,31,32,33,34,35,37,38], low risk of bias in measurement of the outcome were applicable to all of them as these results were usually unaffected by the assessors. For those with CROs, two studied[37,38] blinded the outcome assessors, and they were judged as low risk in this domain, while other studies without the independent assessors were all considered as high risk in bias.

Bias due to missing outcome data and bias in selection of the reported result

The bias due to missing outcome data in four studies were judged as low risk because they were either with very low rate of drop-out, or treated in the proper statistical methods.[33,34,35,37] The

bias in other five studies were considered as high risk as they did not clearly report the drop-out with reasons.[30,32,31,36,38] Regarding the bias in selection of the reported result, only one study registered the protocol and fully reported all the predefined outcomes while other studies did not had registration records nor publish protocols.[30,31,32,33,34,35,36,38]

In summary, the overall judgement as low risk of bias was only applicable to one randomized, double-blinded, placebo-controlled clinical trial as all domains for it were at low risk of bias.[34] Some concerns in the objective outcomes were allocated to two double-blinded RCTs[33,35] and high risk of bias were for the remaining studies. Risk of bias in individual studies were shown Figure 2.

4. Meta-analysis of estimated effect

4.1 Mortality at the end of treatment and follow-ups

A total of six RCTs measured mortality after the treatment of ZFXN preparations.[30,31,32,33,34,38] The homogeneous meta-analysis of mortality suggested that compared with conventional medicine alone, ZFXN as an adjunct treatment reduced the mortality by 41% (RR: 0.54, 95% CI 0.40 to 0.74, I^2=31%, n= 6 RCTs,1060 participants; Figure 3). One study[34] also assessed the mortality in 90-days follow-ups, which suggested that the add-on effect of adjunct ZFXN preparation on reducing the death maintained well (RR: 0.62, 95% CI 0.40 to 0.96, 547 participants). Specific to the placebo-controlled trials, the ZFXN preparation outperformed placebo in the reduction of mortality (RR: 0.16, 95% CI 0.04 to 0.70); however the effect was estimated from a RCT with 103 participants.[38]

Three studies also examined the cause of death,[30,32,34] and the mortality probably resulted from ICH complications including brain hernia, and post hemorrhage pneumonia and recurrent hemorrhage was reduced by 43% in the group with ZFXN preparation compared with the conventional medicine alone (RR: 0.57, 95% CI 0.40 to 0.81, I^2=50%, n=3 RCTs, 810 participants; Supplementary Figure1) .

4.2 Neurological impairments at the end of treatment and follow-ups

A total of six RCTs assessed the neurological impairments of ICH participants after the ZFXN treatment, by using NIHSS (n=6 RCTs)[30,33,34,35,37,38]. Overall, the meta-analysis of NIHSS suggested that the additional use of ZFXN preparations to the conventional medicine reduced the total scores of NIHSS both at the end of treatment (MD:-2.37, 95% CI -3.34 to -1.39, I^2=66%, n=6 RCTs, 994 participants; Figure 4A) and in 90-day follow-ups (MD:-2.85, 95% CI -3.83 to -1.86, I^2=52%, n=3 RCTs, 734 participants; Figure 4B). Specific to the placebo-

controlled trials, ZFXN preparation outperformed placebo in improving neurological impairments measured with NIHSS, at the end of treatment (MD:-2.13, 95% CI -3.34 to -0.92, I^2=75%, n=3 RCTs, 302 participants; Figure 4A) and at 90-day follow-ups (MD:-2.28, 95% CI -3.03 to -1.53, n=1 RCTs, 137 participants; Figure 4B) .

Other scales including MESSS (n=2 RCTs) [30,31], and ESS (n=1 RCTs) [36] were also applied in the evaluation of neurological impairments. A small-scale RCT with MESSS suggested that ZFXN preparation was effective in improving neurological impairments (MD: -4.13, 95% CI -8.25 to -0.01; Supplementary Figure 2). The meta-analysis of these scales in the follow-ups suggested that the effectiveness of ZFXN maintained well in 90 days, as showed in either MESSS (MD:-5.46, 95% CI -7.68 to -3.24, I^2=0%, n=2 RCTs, 83 participants) or ESS (MD: 16.69, 95% CI 13.98 to 19.40, n= 1 RCT, 122 participants; Supplementary Figure 3-4) .

4.3 Dependency

The dependency in terms of BI was measured at the end of the ZFXN treatment (n=3 RCTs) [30,35,37] and in the 90-day follow-up visits (n=5 RCTs).[30,31,35,36,38] Overall, the meta-analysis of BI at the end of treatment suggested that the add-one application of ZFXN preparation in the conventional medicine improved the scores of BI (MD: 13.40, 95% CI 7.50 to 19.29, I^2=55%, n= 3 RCTs, 239 participants; Figure 5A), while the meta-analysis was of moderate heterogeneity. The additional benefits brought by ZFXN preparations to activities of daily living (ADL) maintained well in 90-day follow-ups as shown in a homogeneous meta-analysis (MD: 13.76, 95% CI 11.22 to 16.30, I^2=33%, n=5 RCTs, 431 participants; Figure 5B). Specific to the placebo-controlled trials, the ZFXN preparation outperformed placebo in improving ADL measured with BI, at the end of treatment (MD:14.82, 95% CI 8.79 to 20.82, I^2=61%, n=2 RCTs, 201 participants; Figure 5A) and at 90-day follow-ups (MD:13.31, 95% CI 10.31 to 16.31, I^2=79%, n=2 RCTs, 238participants; Figure 5B) . Another two RCTs assessed the dependency with mRS, and their meta-analysis of homogeneity also showed the add-one effectiveness of ZFXN preparations on improving disability at the end of 90-day follow-ups (MD -1.12, 95% CI -1.33 to -0.90, I^2=0%, n=2 RCTs, 238 participants; Figure 5C).

4.4 The volume of hematoma and perihematomal edema

A total of four RCTs measured the volume of hematoma.[30,31,34,37] The meta-analysis about the volume of hematoma at the end of treatment showed that the additional use of ZFXN preparations provided additional benefits to the conventional medication in reducing the volume of hematoma (MD -3.88 ml, 95% CI -4.87 ml to -2.88 ml, I^2=45%, n=4 RCTs, 694

participants; Figure 6). As there was no minimal clinically important difference (MCID) for the volume of hematoma, its standardised mean difference (SMD) was also computed (SMD -0.74, 95%CI -1.30 to -0.18, I^2=82%, n=4 RCTs, 694 participants). Only one included RCT measured perihematomal edema,[31] which suggested that the perihematomal edema after the 14-day adjunct treatment of ZFXN preparations was not significantly reduced compared with the control group treated with diuretic and dehydration.

4.5 Other analyses

4.5.1 Subgroup-analysis

The subgroup-analyses in terms of sex, age, the baseline characteristics including the volume of hematoma, NIHSS scores and days after the onset of ICH, and the dosage form and therapeutic duration of ZFXN preparation, and inclusion/exclusion of diuretic dehydration suggested that the hematoma volume during the baseline and therapeutic duration affected the post-treatment effectiveness most, across the mortality, neurological impairments measured with NIHSS and ADL assessed with BI. It appeared that the ICH participants with hematoma volume > 20 ml (up to 35ml) and those with the therapeutic duration equal or longer than 28 days benefited most from the ZFXN preparation, and the results were of homogeneity. Table 2 detailed the statistical results of subgroup analyses.

4.5.2 Sensitivity analysis and publication bias

Sensitivity analysis by omitting one study in turn did not alter the results of primary meta-analysis (Supplementary Figure 5 to 10), which suggested the results were robust. Due to the limited number of RCTs included in the meta-analysis, the detection of publication bias was inapplicable to the current data.

5. Safety assessment

A total of seven studies reported the adverse events other than death and current haemorrhage[30,31,33,34,35,37,38]. In general, the meta-analysis of adverse events suggested that the add-one use of ZFXN preparation to the conventional medicine, did not bring additional probability in adverse events (RR: 1.08, 95%CI 0.69 to 1.69, I^2=53%, n=7 RCTs, 1079 participants). Regarding specific types of adverse events, the occurrence of diarrhea was obviously increased (RR 10.02, 95%CI 3.61 to 27.81, I^2 =0%, n= 6 RCTs, 1046 participants), and this was likely caused by *Radix et Rhizoma Rhei*, one of the ingredients of ZFXN, while other types of adverse events were reduced when ZFXN was used, such as electrolyte disorder, hepatic and renal dysfunction, and hypotension (Supplementary Figure 11).

6. GRADE evidence quality

The evidence quality per critical outcomes were graded by GRADE approach (Table 3). The evidence of moderate quality suggested that the adjunct ZFXN preparation provide additional benefits in reducing mortality among the participants with ICH, while the evidence of low quality revealed that the ZFXN in combination with conventional medicine improved neurological impairments of ICH patients.

Discussion

The summary of main findings and strength

This systematic review and meta-analysis of nine RCTs with 1448 participants showed that the adjunct use of ZFXN preparations to conventional medicine in the participants with ICH brought additional benefits to the primary outcomes including mortality and neurological impairments, as well as secondary outcomes including dependency and the volume of cerebral hematoma. Regarding safety, the meta-analysis suggested that though ZFXN did not increase the risk of adverse events in general, though the occurrence of diarrhea was markedly increased. Overall, the present study provided promising evidence for ZFXN preparation in the patients with ICH, either in effectiveness or safety. In almost 20 years from the first publication of ZFXN preparation, though the research and clinical practice of ICH have achieved many progress, RCTs on haemostatic therapies failed to provide supportive evidence on the reduced mortality and improved dependency,[39] and the promising preclinical results of numerous neuroprotective agents have not yet translated into positive clinical trials in patients with ICH.[40] As the focus for treatment of patients after ICH is the prevention of secondary brain damage, and anti-inflammatory and neuro-protective agents are the future research agenda,[41] the promising evidence from ZFXN preparations is encouraging.

Comparison with previous studies and potential pharmacological mechanism

The result in our meta-analysis was generally consistent with a previous systematic review[42] on *"Promoting blood circulation for removing blood stasis therapy"* (PBCRBS) for acute ICH, which showed that PBCRBS interventions used in combination with conventional medicine improved neurological impairments and dependency, as well as reduced the mortality, the volume of hematoma and perihematomal edema. However, conflicting evidences and distinct expert opinions on the safety issue were noted that herbs with the function of PBCRBS might lead to the enlargement of hematoma volume and recurrent haemorrhage. The herbs most frequently reported in the previous meta-analysis[42] was *Sanqi (NOTOGINSENG RADIX ET RHIZOMA)*, has long been used for stroke in Chinese medicine. A laboratory experiment published very early[43] had suggested that the treatment of *Panax notoginseng saponins*, an active ingredient from *Sanqi (NOTOGINSENG RADIX ET RHIZOMA),* worsened the brain edema and neurological functioning when it was applied at the early stage of ICH. Though ZFXN preparations also included *Sanqi (NOTOGINSENG RADIX ET RHIZOMA)*, the duration from the onset was 12.43 hours on average among the included studies, which was safe in general because hematoma expansion mainly occurs within 6 hours of onset which commonly

lead to a quick disease progress in acute ICH.[44] A meta-analysis of *Panax notoginseng saponins (PNS)*,[45] the extract from *Sanqi (NOTOGINSENG RADIX ET RHIZOMA)*, administrated as intravenous drip for ICH, suggested that all the clinical outcomes were remarkably improved without additional risks in safety, when the PNS treatment lasted for at least 28 days and the treatment started within 48 hours after ICH onset, which was similar as the results of subgroup-analysis in the systematic review of ZFXN preparations (Table 2). ZFXN preparations also included *Chuanxiong (CHUANXIONG RHIZOMA)*, another Chinese herb relevant to the PBCRBS principle and the treatment option of priority for headache in Chinese medicine literature,[46] which was reported as a Chinese herb of high frequency in another systematic review[47] on CHM for ICH. This updated meta-analysis[47] including 15 RCTs also demonstrated that CHM with the function of PBCRBS as an adjunct improved neurological impairments in terms of NIHSS and dependency assessed with BI, as well as decreased the cerebral hematoma and edema. Though the pharmacological mechanism on *Chuanxiong (CHUANXIONG RHIZOMA)* for ICH was not fully elucidated, considerable laboratory evidence[48,49] suggested tetramethylpyrazine, an active ingredient from *Chuanxiong (CHUANXIONG RHIZOMA)*, was able to reduce the permeability of blood-brain barrier (BBB) in animal model of traumatic brain injury and in vitro model of ischemia. This might explain its protective role in ICH as the the disruption of BBC was considered essential to the secondary pathophysiology of ICH.[50] However, the safety of *Chuanxiong (CHUANXIONG RHIZOMA)* had not been comprehensively evaluated for ICH patients, which required further research.

Dahuang (Radix et Rhizoma Rhei), another herb in ZFXN preparations, with the function of freeing bowels and expelling stools, represented another therapeutic principle of Chinese medicine for ICH. Laboratory experiments showed that *Dahuang (Radix et Rhizoma Rhei)* and its active ingredients presented protective feature for ICH by multiple pharmacological actions,[51] including protecting the integrity of BBB, reducing the massive cascade of inflammations, inhibiting apoptosis and oxidative stress of the brain tissues, and decreasing lactic acid accumulation at the bleeding location, ultimately to improve the hematoma absorption and edema removal in clinical, which suggested that *Dahuang (Radix et Rhizoma Rhei)* was able to ameliorate the prognosis of ICH by acting both the primary and secondary phases of pathophysiology as complex inflammatory responses were accompanied by the hematoma formation and expansion, and the secondary peri-hematomal edema.[50] Despite the promising evidence of *Dahuang (Radix et Rhizoma Rhei)* for ICH, the event of diarrhea, side effect due to its its original function of freeing bowels and expelling stools was noted.

According to traditional theory of CHM, *Dahuang (Radix et Rhizoma Rhei)* processed by wine was not functioning as a strong laxative. Furthermore, though either raw *Dahuang (Radix et Rhizoma Rhei)* or the processed one was capable of promoting the hematoma absorption and improved neurological impairments,[51] modern experiments showed that the wine-processed one had stronger effect of anti-inflammation in the animal model of ICH than the raw.[52] These evidences should be taken into the consideration in future research to secure the safety utility of ZFXN. *Ginseng (Radix Ginseng)*, was a representative herb to tonify *Qi* in CHM theory, corresponding to the clinical experience proposed by Dr Shaohong Chen, that *Qi* deficiency is essential to acute ICH from the perspective of Chinese medicine. Though the use and potential mechanism of Ginseng for acute ICH was not widely reported and extensively studied, a few in-vivo research suggested[53,54] that active ingredients extracted from *Ginseng (Radix Ginseng)*, including Ginsenoside Rg1, and Ginsenoside Rg2, were capable to ameliorate ICH-induced neurological disorders, probably via modulating the BBB permeability and reducing neuroinflammations in the hemorrhagic hemispheres of animal model.

In summary, the effectiveness of ZFXN preparations for ICH was likely via its protective role in the maintenance of BBC integrity and the reduction of inflammations around the hematomal brain, instead of resolving the haematoma. Differing from *Naoxueshu oral liquid*, other oral Chinese Proprietary Medicine containing leech with the function of anti-coagulation, and inhibiting platelet-aggregation, aiming at resolve the hematoma,[55,56] ZFXN preparations probably protected the individuals with ICH from the secondary injury from hematoma expansion, when brain tissue reacts to hematoma development, and local extra-vascular blood products and peripheral expansion trigger an inflammatory response to disintegrate the hematoma, and vasogenic edema is formed as increased extravasated fluid accumulation due to BBB disruption of endothelial tight junctions.[57]

Evidence completeness and quality

Though this systematic review and meta-analysis provided supportive evidence for the use of ZFXN for acute ICH, we should treat the results cautiously for clinical practice and future research as the evidence certainty was of variety across outcome measures, and evidence incompleteness might exist for some predefined clinical questions. Regarding the primary outcomes, the ZFXN evidence on mortality right after the treatment was of moderate evidence, which suggested that the true effect was likely to be close to the estimate one. As for the neurological impairment, another primary outcome, the ZFXN evidence on NIHSS scores was of low quality, which suggested that our confidence in the effect estimate was limited. One of

the significant factors reducing the evidence quality per NIHSS was the heterogeneity, which was resolved by subgroup-analyses in term of therapeutic duration of ZFXN preparations and the hematoma volume at baseline. And the statistical results implied that the ICH participants with 20-35 ml hematoma volume at baseline and those with the therapeutic duration equal or longer than 28 days benefited most from the ZFXN preparation without any heterogeneity, and the difference between groups was larger than the minimal clinically important difference (MCID) of NIHSS scores in acute stroke patients.[58]

Regarding the secondary clinical outcomes relevant to the dependency of ICH participants, the ZFXN evidence on ADL assessed with BI at the 90-day follow-up visit was of moderate quality, and the mean differences between groups was larger than the MCID of BI in stroke patients,[59] which suggested that this result was of clinical significant alongside with statistical significance. With regard to the secondary biological outcomes, the ZFXN evidence on hematoma volume was of moderate quality, and the estimated SMD was considered representing an effect in moderate magnitude.[60] The evidence on other clinical outcomes such as mRs supported the benefits of ZFXN to ICH patients, but the evidence quality was of low-to-very low due to limited number of studies. The other secondary biological outcome such as perihematomal edema was only reported in one RCT treated with diuretic and dehydration, which failed to examine the primary effectiveness of ZFXN preparation on the reduction of edema.

Limitations and implications for future research

The time-window of CHM treatment including PBCRBSH herbs is a long unresolved question, as hematoma expansion usually occurs in the first 24 hours after ICH, which causes additional death and worse prognosis[61] . Though this meta-analysis of ZFXN preparation identified the optimal administration timing potentially beneficial to all clinical outcomes, its precise time window was uncertain. The subgroup-analysis suggested that the participants with an clinical presentation within 72 hours after an onset of ICH was able to benefit from the ZFXN treatment generally; however, the risk of recurrent ICH within 24 hours after onset was uncertain clinically due to the limited information of safety assessment and the lack of measuring non-fatal recurrent ICH. In addition, the increase of perihematomal edema during 72 hours was associated with worse functional outcomes after ICH[62] ; however, the included RCTs seldom reported the condition of perihematomal edema before-and-after treatments of ZFXN. Previous evidence showed that the lobar ICH location was associated with a higher risk of recurrent ICH[63]; but most of the ZFXN RCTs included the cases with other bleeding locations alongside with basal ganglia ICH, which might cause heterogeneity in effectiveness and harm. These

clinical questions should be considered in the methodological design and statistical analysis plan of future RCTs. Regarding safety, the increased occurrence of diarrhoea probably due to ZFXN was noted. Previous studies identified the high prevalence of constipation after ICH and proposed the necessity of laxative therapy[64-65] . *Dahuang (Radix et Rhizoma Rhei)* in ZFXN preparation seems appropriate for the ICH participants with concurrent constipation as it is a common herb with laxative effect without known toxicity. However, whether an increased occurrence of diarrhoea was beneficial or harmful to the acute ICH patients without constipation remained unknown. An prior statistical analysis plan considering this subgroup participants should be considered in future RCTs.

As the current evidence was from small and exploratory RCTs, a multi-site, larger sample, confirmatory RCT with improved methodological design, better quality control, and reporting adherence to CONSORT Extension for Chinese Herbal Medicine Formulas [66] was needed . An ongoing multicenter, prospective, randomized, double-blind clinical trial--the CHAIN trial (Clinicaltrials.gov: NCT05066620) slated for completion recently will hopefully fill in the gap [67] .

Conclusion

Clinical evidence of low-to-moderate quality suggested that adjunct ZFXN preparation was potentially effective and safe for acute ICH. However, a multi-site, larger sample, confirmatory RCT with improved methodological design and quality control was needed, before its comparative research with other proprietary Chinese medicine.

Acknowledgement

None.

Funding

This research was funded by the Key-Area Research and Development Program of Guangdong Province (No. 2020B1111100009), the National Natural Science Foundation of China (No. 81974559), the Natural Science Foundation of Guangdong Province (No. 2020A1515010992), and the Xinglin Scholar Research Premotion Project of Chengdu University of TCM (No. XKTD2021004).

Conflicts of interest

None.

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Figures

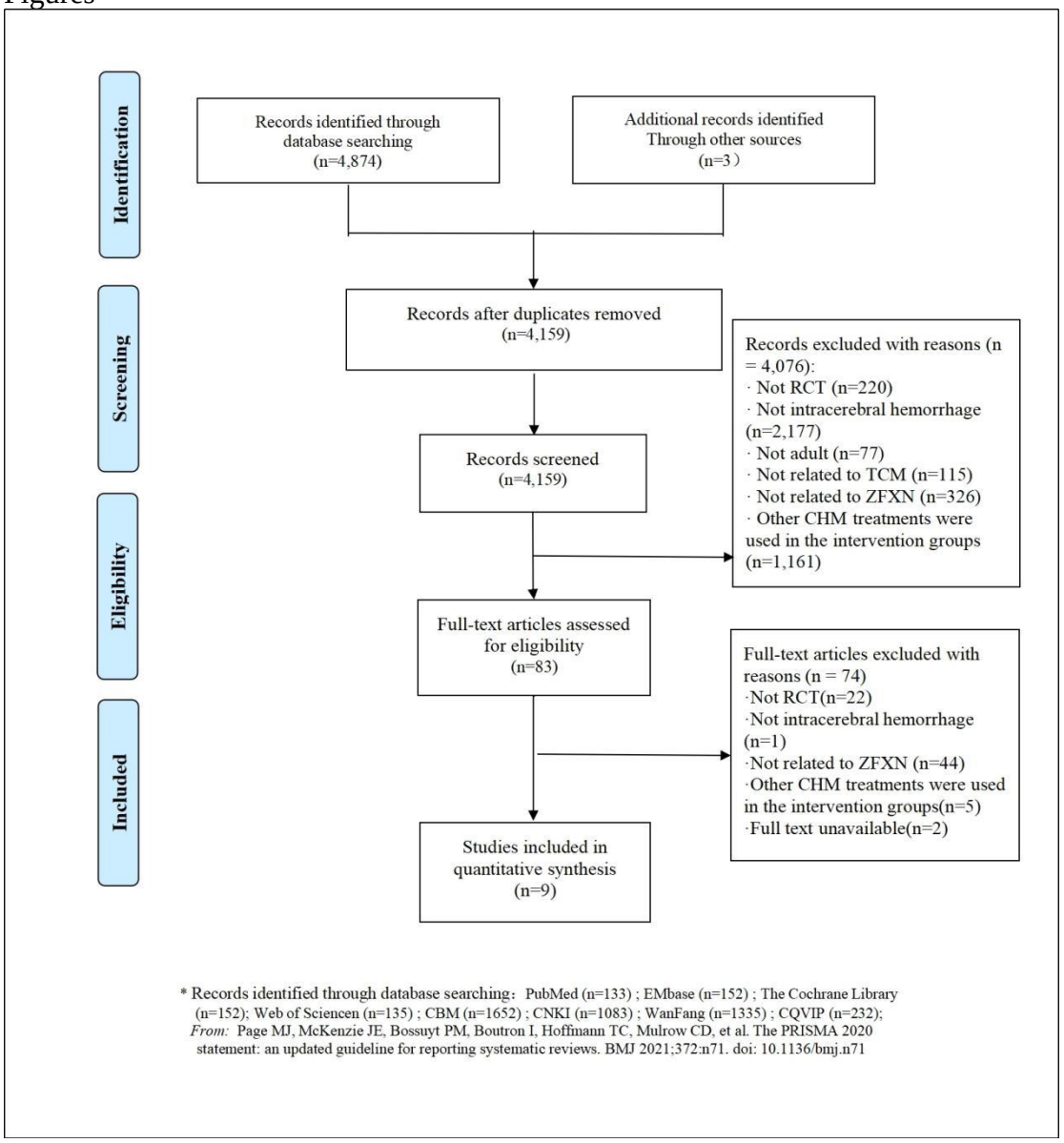


Figure 1. Flowchart of literature screening.

CHM: Chinese Herbal Medicine; RCT: Randomized Clinical Trial; TCM: Traditional Chinese Medicine; ZFXN: Zhongfeng Xingnao preparations.

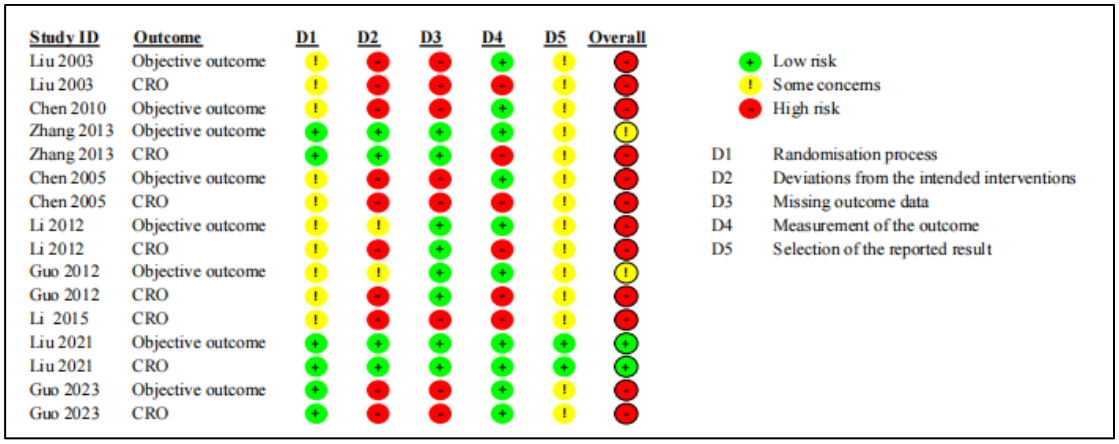


Figure 2. Risk of bias of included studies.

D1: bias arising from the randomization process; D2: bias due to deviations from intended interventions; D3: due to missing outcome; D4: bias in measurement of the outcome; D5: bias in selection of the reported result. CRO: clinician-reporting outcome.

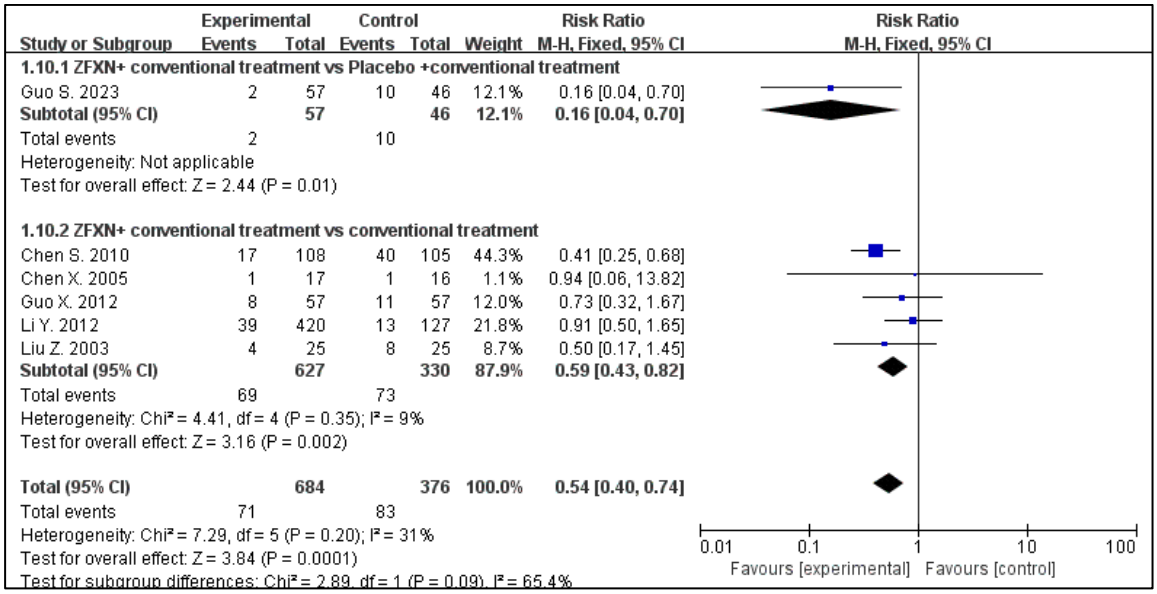
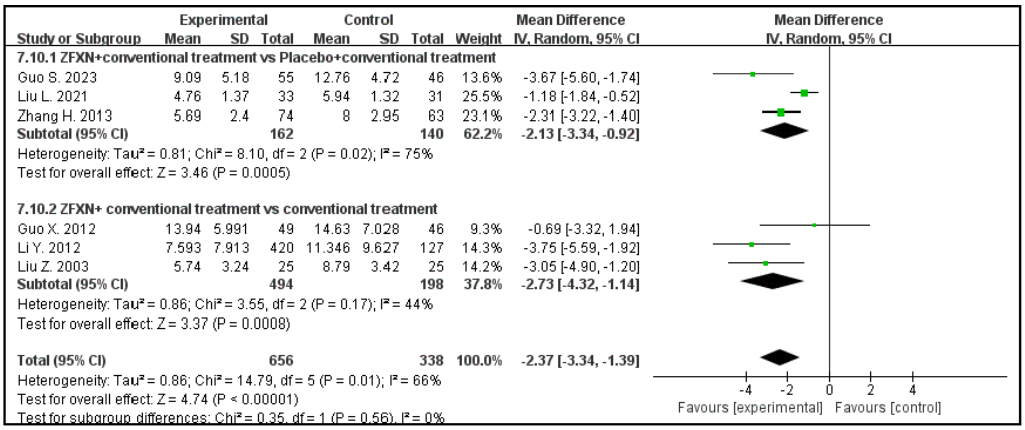


Figure 3. The forest plot of mortality at the end of treatment.

A



B

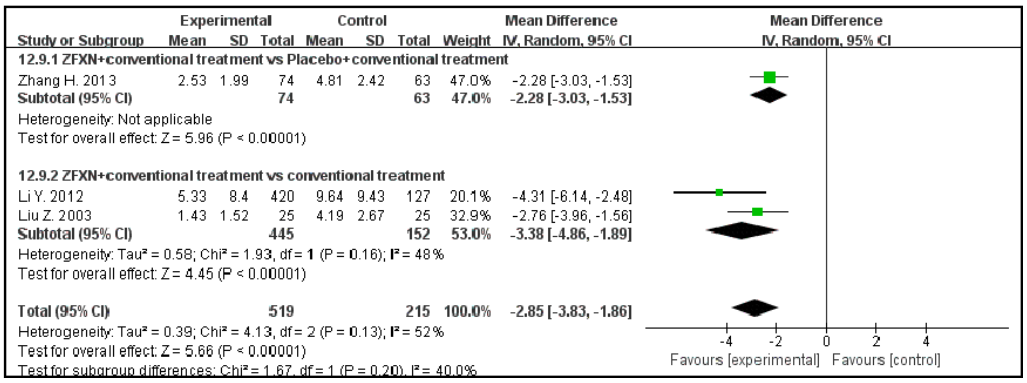


Figure 4. The forest plot of NIHSS

A. at the end of treatment, B. at the end of follow-ups

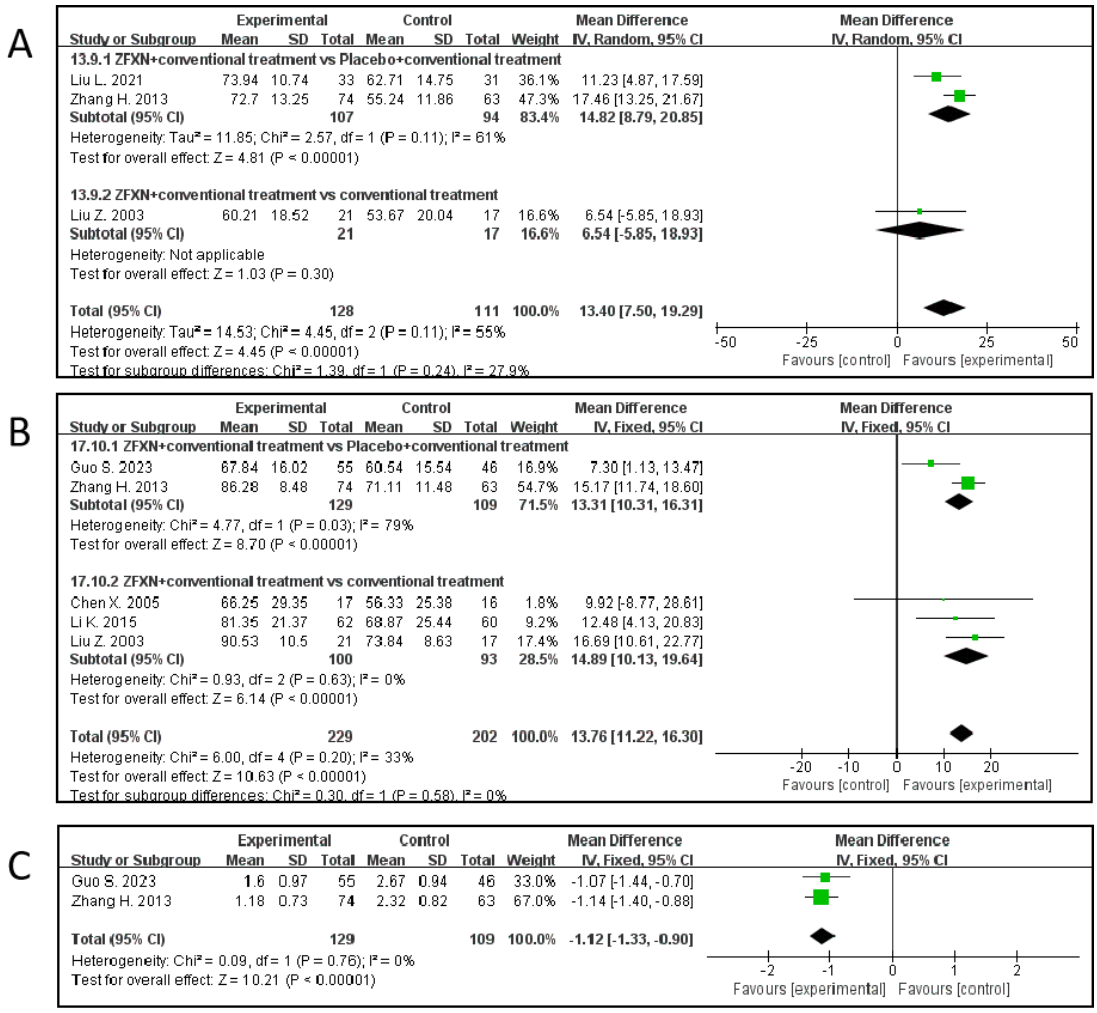


Figure 5. The forest plot of dependency

A. Barthel Index (BI) at the end of treatment, B. BI at the end of 90-day follow-ups, C. modified Rankin Scale (mRS) at the end of 90-day follow-ups.

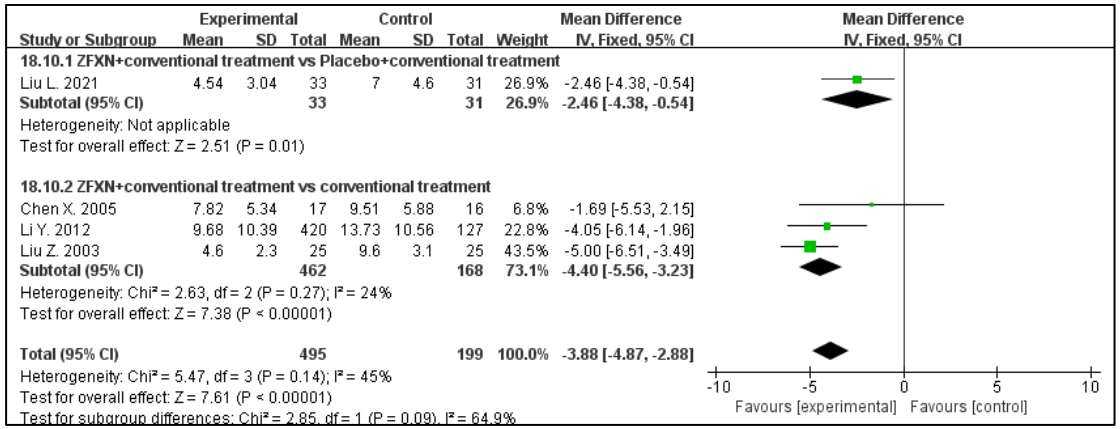


Figure 6. The forest plot of hematoma volume at the end of treatment.

Table 1. Basic characteristics of included studies

Study	Sample size	Age, y mean (sd)	Sex, M/F	Time of onset , hours, mean (sd)	Disease severity, mean (sd)	Intervention			Control	Outcome
						Treatment	Form, Dosage, administration	Course		
Liu Z, 2003	50	T: 60.5 (9.11) C: 62.9 (5.45)	T : 15/10 C : 14/11	< 48h	NIHSS: T:12.50 (4.10) C:12.76 (4.07)	ZFXN+CM	Oral solution, 30ml q6h,by nasogastric tube	30d	Diuretic dehydration+ CM	Death, NIHSS, Hematoma volume, BI, Adverse events
Chen S, 2010	225	T: 68.12 C: 68.12	NS	< 72h	NHISS: NS	ZFXN+CM	Oral solution, 25ml q6h, by nasogastric tube	28d	Diuretic dehydration+ CM	Death, Hematoma volume, Adverse events
Zhang H, 2013	164	T: 63.7 (7.95) C: 63.68 (7.55)	T: 49/34 C: 48/33	T: 12.21 (16.22) C: 9.77 (10.15)	NHISS: T:21.9 (7.37) C:22.19 (8.24)	ZFXN+Diuretic dehydration+CM	Decoction, 50ml q6h, by nasogastric tube	28d	Placebo, Diuretic dehydration+ CM	Death, NIHSS, Hematoma volume, BI, mRS
Chen X, 2005	38	T: 63.18 (7.90) C: 64.69 (8.16)	NS	T 8.03 (1.09) C: 7.84 (1.09)	NHISS: NS	ZFXN+Diuretic dehydration+CM	Oral solution, 30ml q6h, by nasogastric tube	14d	Diuretic dehydration+ CM	Death, MESSS, Hematoma volume, BI, Adverse events
Li Y, 2012	547	T: 66.13 (9.25) C: 66.06 (8.88)	T: 150/270 C: 46/81	T: 12.51 (18.64) C: 12.45 (17.64)	NIHSS: T: 20.77(7.68) C: 21.87(8.17)	ZFXN+Diuretic dehydration+CM	Decoction, 50ml q6h, by nasogastric tube	21d	Diuretic dehydration+ CM	Death, NIHSS, Hematoma volume, Adverse events
Guo X, 2012	114	T: 66.37 (10.19) C: 66.75 (9.36)	T:34/23 C:31/26	T: 16.16 (18.99) C: 14.72 (16.62)	NIHSS: T: 30.82(6.55) C: 31.28(6.95)	ZFXN+Diuretic dehydration+CM	Oral solution, 25ml q6h oral administration/ng	7d	Diuretic dehydration+ CM	Death, NIHSS
Li K, 2015	122	T: 69.63 (11.35) C: 71.34 (12.21)	T:33/29 C:32/28	< 72h	NS	ZFXN+Diuretic dehydration+CM	Oral solution, 25ml q6h,by nasogastric tube	28d	Diuretic dehydration+ CM	ESS, BI,Adverse events

Liu L, 2021	70	T:68 C:62	T:17/18 C:19/16	T: 9 C: 6	NIHSS: T: 11.49(3.67) C: 12.17(2.19)	ZFXN+Diuretic dehydration+CM	Granule, 8g q8h, by nasogastric tube	21d	Placebo,Diuretic dehydration+CM	NIHSS,Hematoma volume, BI, Adverse events
Guo S, 2023	118	T: 68.93 (5.18) C: 65.57 (11.73)	NS	< 48h	NIHSS: T:16.40(4.81) C:16.20(4.54)	ZFXN+Surgery +Diuretic dehydration+CM	Oral solution, 25ml q6h, administration by nasogastric tube	28d	Placebo,Surgery+Diuretic dehydration+CM	Death, NIHSS, Hematoma volume, BI, mRS, Adverse events

Notes: For studies without the data in the forms of mean (standard deviation), information in their original forms were presented. Abbreviations: BI: Barthel index ,d: day, h: hour, NIHSS:National Institute of Health stroke scale; mRs: modified Rankin scale, NS: not stated, sd:standard deviation, y: year.

Table 2. Subgroup-analyses in terms of Mortality, National Institute of Health stroke, Barthel index and Hematoma volume

Mortality				
Subgroup	RCTs, No	Total patients, No	RR (95% CI)	I^2, %
Sex				
the proportion of male ≤50%	3	683	0.65 [0.39, 1.09]	58
the proportion of male＞50%	3	377	0.48 [0.33, 0.72]	0
Age				
≤65	2	83	0.55 [0.21, 1.47]	0
＞65	4	977	0.54 [0.39, 0.75]	58
Hematoma volume				
≤ 20ml	2	580	0.91 [0.51, 1.63]	0
＞20ml	3	366	0.38 [0.25, 0.58]	0
Baseline NIHSS				
≤15	1	50	0.50 [0.17, 1.45]	/
＞15	3	764	0.66 [0.43, 1.04]	57
Timing of enrollment				
＜48h	2	153	0.24 [0.09, 0.64]	18
＜72h	2	327	0.39 [0.22, 0.66]	51
＜1w	1	547	0.90 [0.46, 1.74]	13
Dosage form				
oral liquid	5	513	0.44 [0.30, 0.64]	0
decoction	1	547	0.91 [0.50, 1.65]	/
Therapeutic duration				
＜28 days	3	694	0.85 [0.53, 1.36]	0
≥28 days	3	366	0.38 [0.25, 0.58]	0
Diuretic dehydration				
Exclude	2	263	0.43 [0.27, 0.67]	0
Include	4	797	0.67 [0.43, 1.04]	36

NIHSS				
Subgroup	RCTs, No	Total patients, No	MD [95% CI]	I^2, %
Overall	6	994	-2.37 [-3.34, -1.39]	
Sex				
the proportion of male≤50%	2	648	-3.71 [-5.05, -2.38]	0
the proportion of male＞50%	4	346	-1.82 [-2.74, -0.90]	55
Age				
≤65	2	187	-2.45 [-3.27, -1.64]	0
＞65	4	807	-2.31 [-3.92, -0.69]	74

Hematoma volume				
≤20ml	2	611	-2.32 [-4.82, 0.19]	85
＞20ml	3	288	-2.64 [-3.39, -1.89]	0
Baseline NIHSS				
≤15	2	114	-1.91 [-3.69, -0.12]	71
＞15	4	880	-2.70 [-3.80, -1.60]	41
Timing of enrollment				
＜24h	1	63	-1.18 [-1.84, -0.52]	/
＜48h	2	151	-3.35 [-4.68, -2.01]	0
＜72h	2	232	-2.14 [-3.00, -1.28]	23
＜1w	1	547	-3.75 [-5.59, -1.92]	/
Dosage form				
Oral liquid	3	246	-2.69 [-4.25, -1.13]	40
Granula	1	64	-1.18 [-1.84, -0.52]	/
Decoction	2	684	-2.80 [-4.14, -1.46]	47
Therapeutic duration				
＜28 days	3	706	-1.88 [-3.65, -0.11]	71
≥28 days	3	288	-2.64 [-3.39, -1.89]	0
Diuretic dehydration				
Exclude	1	50	-3.05 [-4.90, -1.20]	/
Include	5	944	-3.05 [-4.90, -1.20]	70
BI				

Subgroup	RCTs, No	Total patients, No	MD [95% CI]	I^2, %
Sex				
the proportion of male≤50%	2	134	7.56 [1.70, 13.42]	0
the proportion of male＞50%	3	297	15.19 [12.38, 18.00]	0
Age				
≤65	3	208	15.40 [12.45, 18.35]	0
＞65	2	223	9.13 [4.17, 14.09]	0
Hematoma volume				
≤20ml	1	33	9.92 [-8.77, 28.61]	/

＞20ml	4	398	13.83 [11.27, 16.39]	49
Baseline NIHSS				
≤15	1	38	16.69 [10.61, 22.77]	/
＞15	2	238	11.67 [4.01, 19.34]	79
Timing of enrollment				
＜48h	2	139	12.06 [7.73, 16.40]	78
＜72h	2	259	14.78 [11.61, 17.95]	0
Dosage form				
Oral liquid	4	294	12.06 [8.29, 15.83]	34
Decoction	1	137	15.17 [11.74, 18.60]	/
Therapeutic duration				
＜28 days	1	33	9.92 [-8.77, 28.61]	/
≥28 days	4	398	13.28 [9.32, 17.25]	49
Diuretic dehydration				
Exclude	1	38	16.69 [10.61, 22.77]	/
Include	4	393	13.14 [10.35, 15.93]	39
Hematoma volume (ml)				
Subgroup	RCTs, No	Total patients, No	MD [95% CI]	I^2, %
Overall	4	694	-3.88 [-4.87, -2.88]	45
Sex				
the proportion of male≤50%	2	580	-3.51 [-5.35, -1.68]	11
the proportion of male＞50%	2	114	-4.03 [-5.22, -2.84]	76
Age				
≤65	2	83	-4.56 [-5.96, -3.15]	60
＞65	2	611	-3.19 [-4.60, -1.78]	17
Hematoma volume				
≤20ml	3	644	-3.01 [-4.34, -1.68]	0
＞20ml	1	50	-5.00 [-6.51, -3.49]	/
Baseline NIHSS				
≤15	2	114	-4.03 [-5.22, -2.84]	76
＞15	1	547	-4.05 [-6.14, -1.96]	/
Timing of enrollment				
＜24h	1	64	-2.46 [-4.38, -0.54]	/
＜48h	1	50	-5.00 [-6.51, -3.49]	/
＜1w	1	547	-4.05 [-6.14, -1.96]	/
Dosage form				
Oral liquid	2	83	-4.56 [-5.96, -3.15]	60
Granula	1	64	-2.46 [-4.38, -0.54]	/
Decoction	1	547	-4.05 [-6.14, -1.96]	/
Therapeutic duration				
＜28 days	3	655	-3.01 [-4.34, -1.68]	0
≥28 days	1	50	-5.00 [-6.51, -3.49]	/
Diuretic dehydration				
Exclude	1	50	-5.00 [-6.51, -3.49]	/
Include	3	644	-3.01 [-4.34, -1.68]	0

Notes: BI: Barthel index, NIHSS:National Institute of Health stroke scale, mRs: modified Rankin scale.

Table 3. GRADE evidence quality of critical outcomes

Mortality (post-treatment)									
ZFXN + conventional medicine vs. control									
Quality assessment					No. of patients		Relative effect	Certainty	Importance
No. of Trails	Risk of bias	Inconsistency	Indirectness	Imprecision	ZFXN	control	RR (95% CI)		
6 RCTs	serious	not serious	not serious	not serious	684	376	0.54 (0.40 to 0.74)	⊕⊕⊕◯ Moderate	CRITICAL
NIHSS scores (post-treatment)									
ZFXN + conventional medicine vs. control									
Quality assessment					No. of patients		Relative effect	Certainty	Importance
No. of Trails	Risk of bias	Inconsistency	Indirectness	Imprecision	ZFXN	control	MD (95% CI)		
6 RCTs	serious	serious	not serious	not serious	656	338	-2.37 (-3.34 to -1.39)	⊕⊕◯◯ Low	CRITICAL
NIHSS scores (follow-ups)									
ZFXN + conventional medicine vs. control									
Quality assessment					No. of patients		Relative effect	Certainty	Importance
No. of Trails	Risk of bias	Inconsistency	Indirectness	Imprecision	ZFXN	control	MD (95% CI)		
3 RCTs	serious	serious	not serious	not serious	519	215	-2.85 (-3.83 to -1.86)	⊕⊕◯◯ Low	CRITICAL
Barthel Index (follow-ups)									
ZFXN + conventional medicine vs. control									
Quality assessment					No. of patients		Relative effect	Certainty	Importance
No. of Trails	Risk of bias	Inconsistency	Indirectness	Imprecision	ZFXN	control	MD (95% CI)		

5 RCTs	serious	not serious	not serious	not serious	229	202	13.76 (11.22, 16.30)	⊕⊕⊕◯ Moderate	CRITICAL
Hematoma volume (post treatment)									
ZFXN + conventional medicine vs. control									
Quality assessment					No. of patients		Relative effect	Certainty	Importance
No. of Trails	Risk of bias	Inconsistency	Indirectness	Imprecision	ZFXN	control	MD (95% CI)		
4 RCTs	serious	not serious	not serious	not serious	495	199	-3.88 (-4.87, -2.88)	⊕⊕⊕◯ Moderate	CRITICAL

The supplementary tables

- Supplementary Table1. Search strategies.
- Supplementary Figure 1. The forest plot of case fatality at the end of treatment.
- Supplementary Figure 2. The forest plot of MESSS at the end of ZFXN treatment
- Supplementary Figure 3. The forest plot of MESSS in 90 days follow-ups.
- Supplementary Figure 4. The forest plot of ESS in 90 days follow-ups.
- Supplementary Figure 5. The sensitivity analysis of mortality at the the end of ZFXN treatment.
- Supplementary Figure 6. The sensitivity analysis of NIHSS at the the end of ZFXN treatment.
- Supplementary Figure 7. The sensitivity analysis of NIHSS in 90-day follow-ups.
- Supplementary Figure 8. The sensitivity analysis of BI at the the end of ZFXN treatment.
- Supplementary Figure 9. The sensitivity analysis of BI in 90-day follow-ups.
- Supplementary Figure 10. The sensitivity analysis of hmatoma volume at the end of ZFXN treatment.
- Supplementary Figure 11. The forest plot of adverse events

Supplementary materials

Supplementary Table1. Search strategies.

■□ PubMed search strategy #1 "Cerebral Hemorrhage"[MeSH Terms] OR "intracranial hemorrhage, hypertensive"[MeSH Terms] OR "Hemorrhagic Stroke"[MeSH Terms] #2 (((Fossa* OR Intracranial* OR Brain* OR Cerebr*) AND (Hemorrhage* OR Hematoma*)) OR ICH OR ICHs) # 3 #1 OR #2 #4 "Medicine, Chinese Traditional"[Mesh] OR "Drugs, Chinese Herbal"[Mesh] OR "Plants, Medicinal"[Mesh] OR "Herbal Medicine"[Mesh] #5 ((((((((((Traditional Chinese Medicine) OR (Traditional Medicine, Chinese)) OR (Chinese Traditional Medicine)) OR (Chinese Medicine, Traditional)) OR (Chinese Herbal Drugs)) OR (Herbal Drugs, Chinese)) OR (Herbal formulation)) OR (Fuyuan Xingnao Decoction)) OR (Fuyuan Xingnao oral liquid)) OR (Zhongfeng Xingnao oral liquid)) OR (Zhongfeng Xingnao Decoction)) OR (Zhuyu Huatan Decoction)) OR (Zhuyu Huatan oral liquid) #6 #4 OR #5 # 7 randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract] # 8 #7 AND #3 AND #6
■□ Cochrane search strategy #1 cerebral hemorrhage #2 intracranial hemorrhage, hypertensive #3 hemorrhagic stroke #4 (((Fossa* or Intracranial* or Brain* or Cerebr*) and (Hemorrhage* or Hematoma*)) or ICH or ICHs) .tw #5 #1 OR #2 OR #3 OR #4 #6 Medicine, Chinese Traditional #7 Drugs, Chinese Herbal #8 Plants, Medicinal #9 Herbal Medicine #10 (Traditional Chinese Medicine):ab,ti,kw OR (Traditional Medicine, Chinese):ab,ti,kw OR (Chinese Traditional Medicine):ab,ti,kw OR (Chinese Medicine, Traditional):ab,ti,kw OR (Chinese Herbal Drugs):ab,ti,kw OR (Herbal Drugs, Chinese):ab,ti,kw OR (Herbal formulation):ab,ti,kw OR (Fuyuan Xingnao Decoction):ab,ti,kw OR (Fuyuan Xingnao oral liquid):ab,ti,kw OR (Zhongfeng Xingnao oral liquid):ab,ti,kw OR (Zhongfeng Xingnao Decoction):ab,ti,kw OR (Zhuyu Huatan Decoction):ab,ti,kw OR (Zhuyu Huatan oral liquid):ab,ti,kw #11 #6 OR #7 OR #8 OR #9 OR #10 #12 (randomized controlled trial):ab,ti,kw OR (randomized):ab,ti,kw OR (placebo):ab,ti,kw OR (RCT):ab,ti,kw #13 #5 AND #11 AND #12
■□ Embase search strategy #1 cerebral hemorrhage #2 intracranial hemorrhage, hypertensive #3 hemorrhagic stroke #4 ('fossa*':ab,ti OR 'intracranial*':ab,ti OR 'brain*':ab,ti OR 'cerebr*':ab,ti) AND ('hemorrhage*':ab,ti OR 'hematoma*':ab,ti) OR ('ich':ab,ti OR 'ichs':ab,ti) #5 Medicine, Chinese Traditional #6 Drugs, Chinese Herbal

#7 Plants, Medicinal
#8 Herbal Medicine
#9 'Traditional Chinese Medicine':ab,ti OR 'Traditional Medicine, Chinese':ab,ti OR 'Chinese Traditional Medicine':ab,ti OR 'Chinese Medicine, Traditional':ab,ti OR 'Chinese Herbal Drugs':ab,ti OR 'Herbal Drugs, Chinese':ab,ti OR 'Herbal formulation':ab,ti OR 'Fuyuan Xingnao Decoction':ab,ti OR 'Fuyuan Xingnao oral liquid':ab,ti OR 'Zhongfeng Xingnao oral liquid':ab,ti OR 'Zhongfeng Xingnao Decoction':ab,ti OR 'Zhuyu Huatan Decoction':ab,ti OR 'Zhuyu Huatan oral liquid':ab,ti
#10 'randomized controlled trial':ab,ti OR 'randomized':ab,ti OR 'placebo':ab,ti OR 'RCT':ab,ti
#11 #1 OR #2 OR #3 OR #4
#12 #5 OR #6 OR #7 OR #8 OR #9
#13 #10 AND #11 AND #12

■□ Web of Science search strategy
#1 TS=(Cerebral hemorrhage OR Hemorrhagic Stroke OR Intracranial Hemorrhage, Hypertensive OR ICH OR ices) OR TS=((Fossa* OR Intracranial* OR Brain* OR Cerebr*) AND (Hemorrhage* OR Hematoma*))
#2 TS=(Medicine, Chinese Traditional OR Drugs, Chinese Herbal OR Plants, Medicinal OR Herbal Medicine OR Traditional Chinese Medicine OR Traditional Medicine, Chinese OR Chinese Traditional Medicine OR Chinese Medicine, Traditional OR Chinese Herbal Drugs OR Herbal Drugs, Chinese OR Herbal formulation OR Fuyuan Xingnao Decoction OR Fuyuan Xingnao oral liquid OR Zhongfeng Xingnao oral liquid OR Zhongfeng Xingnao Decoction OR Zhuyu Huatan Decoction OR Zhuyu Huatan oral liquid)
#3 TS=(randomized controlled trial OR randomized OR placebo OR RCT)
#4 #1 AND #2 AND #3

Chinese search strategy

1. intracranial hemorrhage

1.1 Mesh term

脑出血；颅内出血；壳核出血；脑出血, 创伤性；颅内出血, 高血压性；中风；卒中；脑血管基底神经节出血；脑血管障碍

1.2 Entry term

高血压性脑出血；脑血管疾病；高血压病脑出血；脑血管意外；急性脑血管病；脑实质内出血；脑中风；急性脑血管意外；急性脑血管病；脑溢血；脑血管病；脑血管病变；卒中；脑卒中；出血性脑卒中；出血性中风；出血性卒中；出血性脑中风；高血压脑出血；基底节区脑出血；基底节出血；基底节脑出血；基底节核区脑出血；

2. Zhongfeng xingnao

2.1 Mesh term

中成药；中药；中草药；中医学

2.2 Entry term

院内制剂；成方制剂；中风醒脑；中风醒脑液；中风醒脑口服液；中风醒脑方；中风醒脑合剂；中风醒脑复方；中风醒脑汤；中风醒脑胶囊；复元醒脑；复元醒脑汤；复元醒脑方；复元醒脑口服液；复元醒脑颗粒；复元醒脑法；逐

瘀化痰；逐瘀化痰口服液；逐瘀化痰**汤**；逐瘀化痰方；逐瘀化痰法；逐瘀化痰丸；中医；中西医；中西医**结**合；

3. RCT

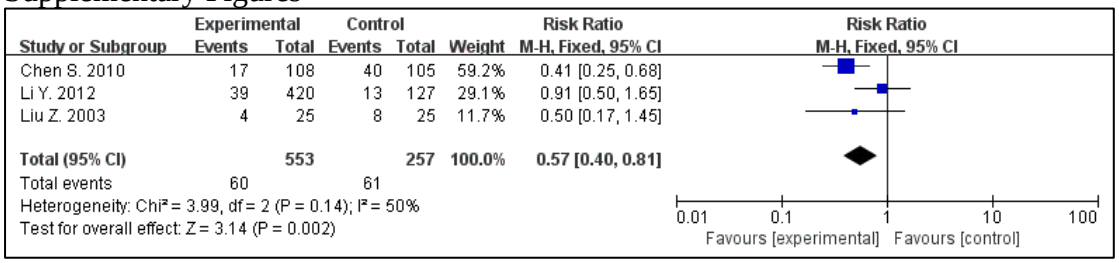
3.1 Mesh term

随机**对**照**试验**

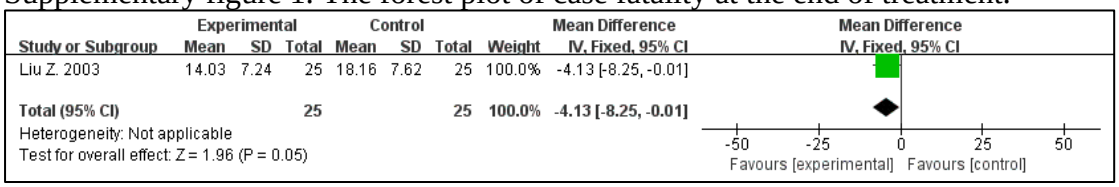
3.2 Entry term

随机**对**照；RCT；随机**对**照**实验**；随机**对**照研究；随机

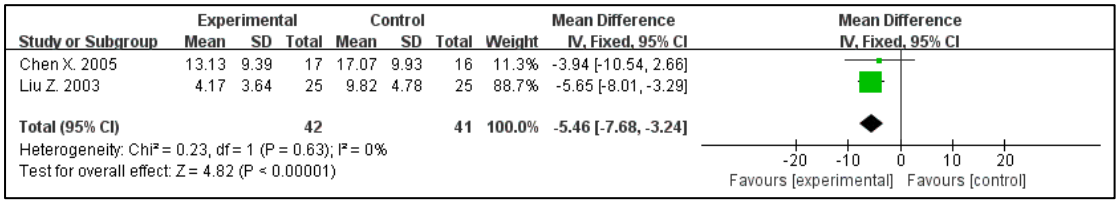
Supplementary Figures



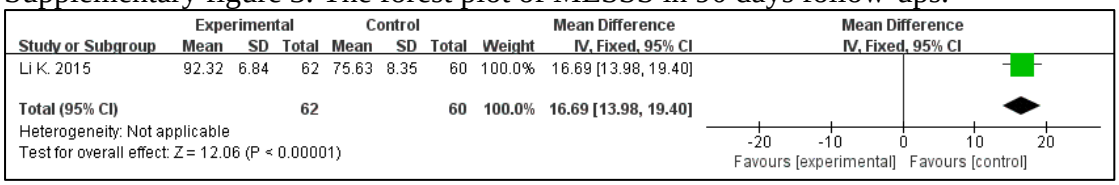
Supplementary figure 1. The forest plot of case fatality at the end of treatment.



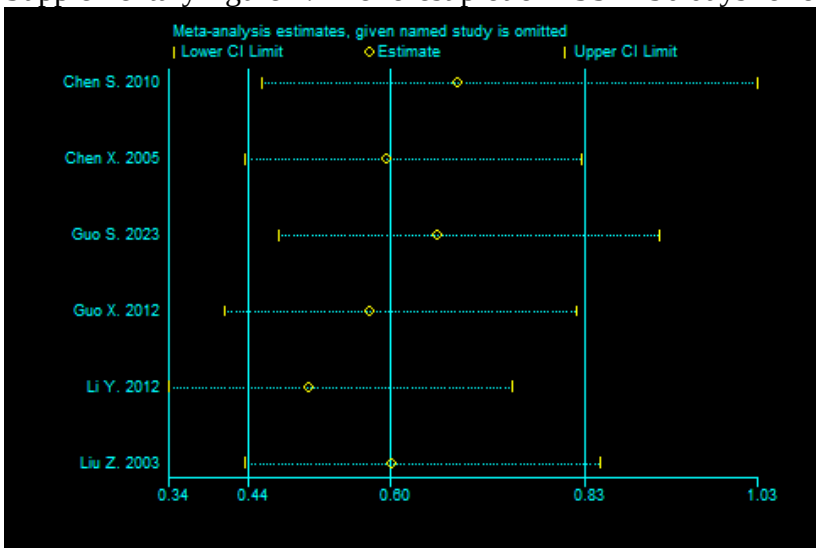
Supplementary figure 2. The forest plot of MESSS at the end of ZFXN treatment



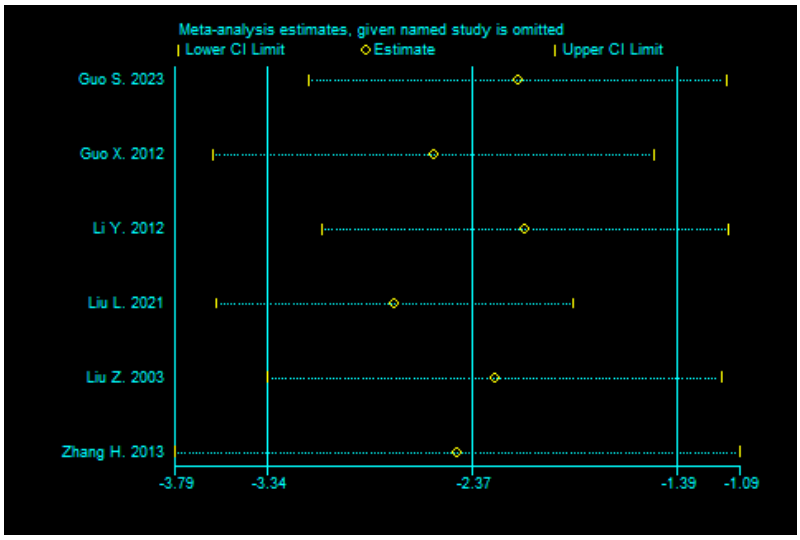
Supplementary figure 3. The forest plot of MESSS in 90 days follow-ups.



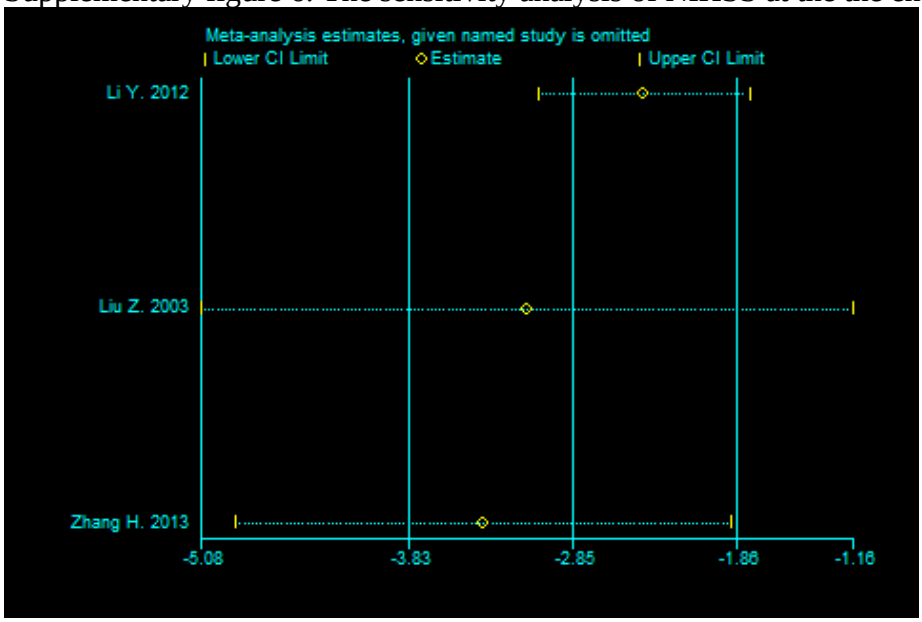
Supplementary figure 4. The forest plot of ESS in 90 days follow-ups.



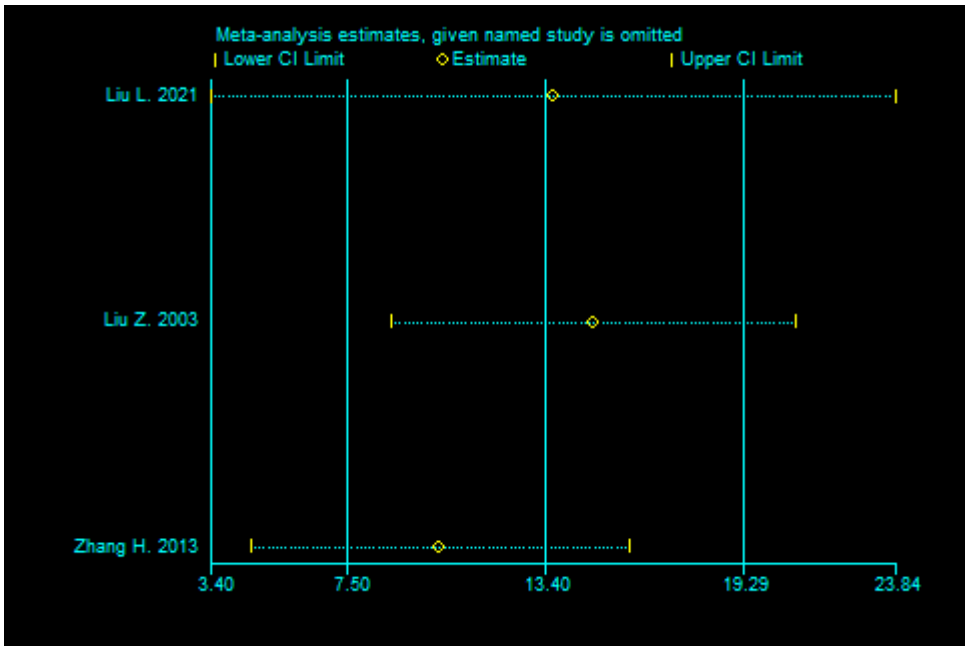
Supplementary figure 5. The sensitivity analysis of mortality at the the end of ZFXN treatment.



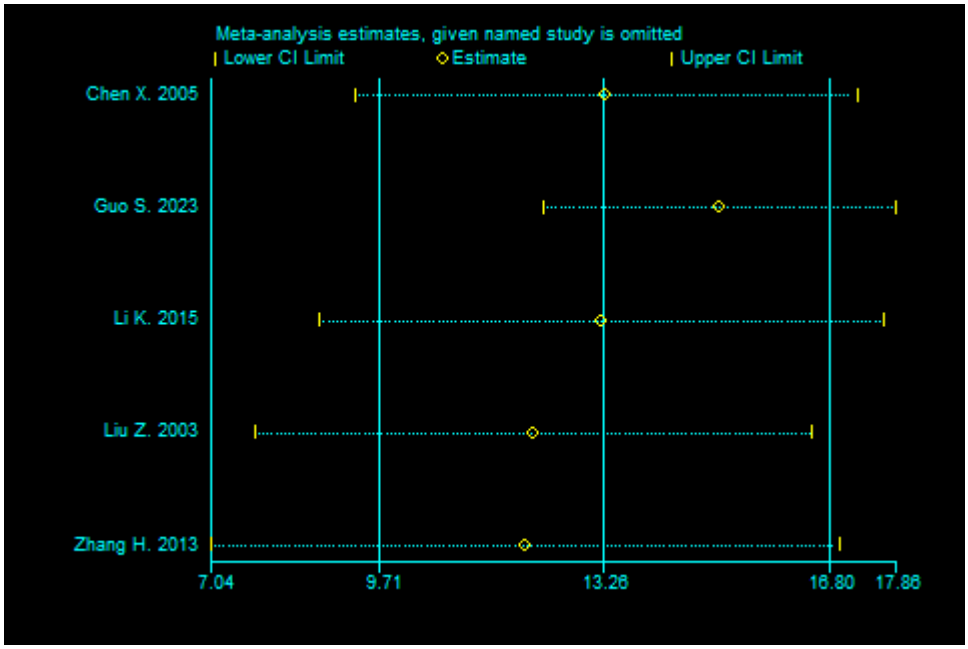
Supplementary figure 6. The sensitivity analysis of NIHSS at the the end of ZFXN treatment.



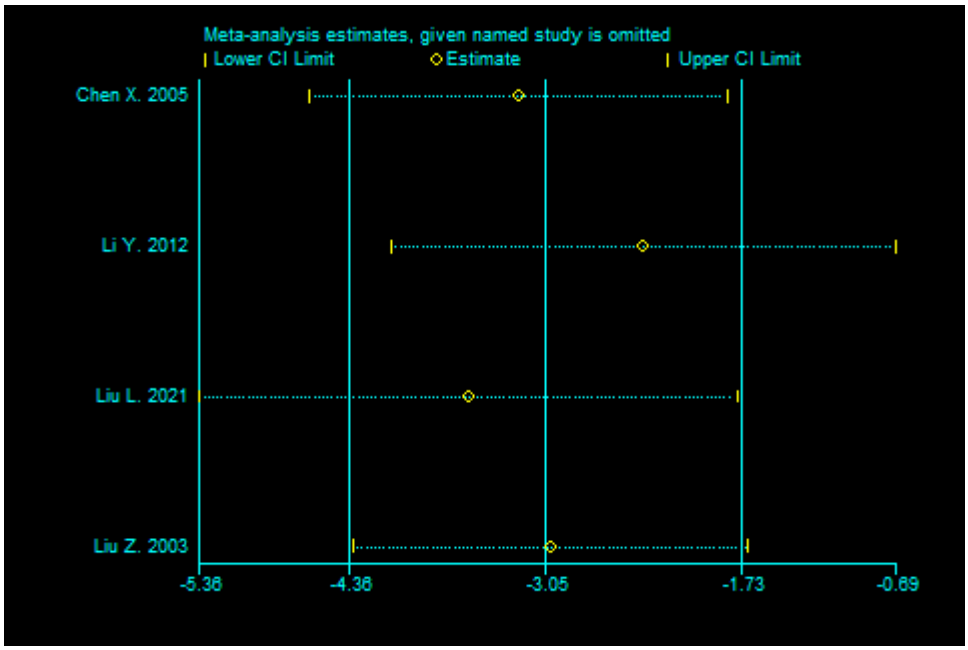
Supplementary figure 7. The sensitivity analysis of NIHSS in 90-day follow-ups.



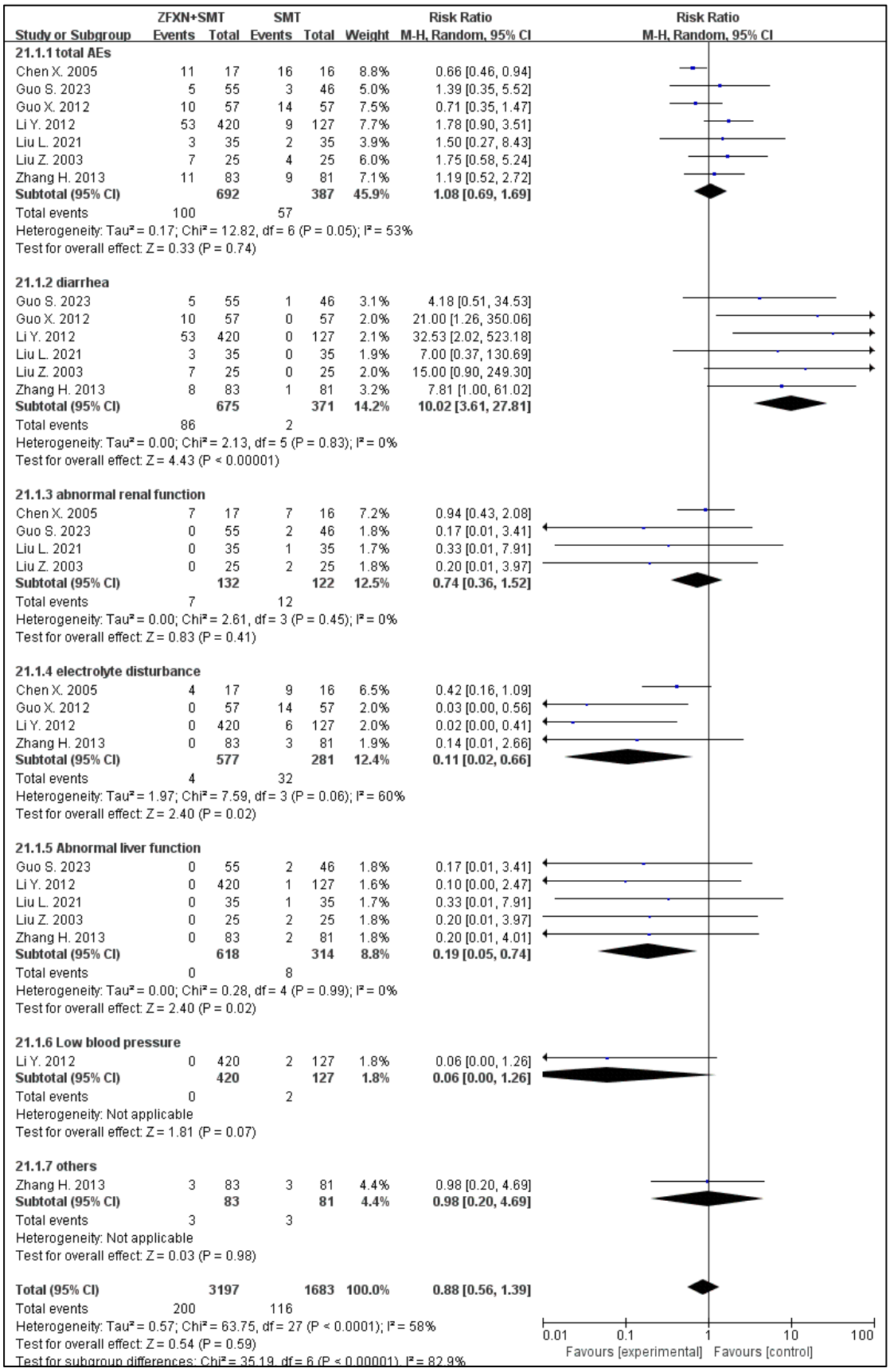
Supplementary figure 8. The sensitivity analysis of BI at the the end of ZFXN treatment.



Supplementary figure 9. The sensitivity analysis of BI in 90-day follow-ups.



Supplementary figure 10. The sensitivity analysis of hmatoma volume at the end of ZFXN treatment.



Supplementary figure 11. The forest plot of adverse events

Chinese Herbal medicine in Acute INtracerebral haemorrhage (CHAIN) trial

INVESTIGATOR AGREEMENT

[illegible]

Protocol Title: Chinese Herbal medicine in Acute INtracerebral haemorrhage (CHAIN) trial

Version and Date: [illegible]

[illegible]

Investigator's Signature Date (Day / Month / Year)

[illegible]

[illegible]

Principal Investigator

Co-Principal Investigator

[illegible]

	Date	*Signature*

Co-Principal Investigator

[illegible]

	24 September 2021	
		Signature
	Date	

Trial Statistician

Mr□□□ □□□□□□□□□

□□□□□□ □□r□□□□□□□□□□□□□□□□□r□□□ □□□□□□□

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□

Date *Signature*

CONTENTS

1. ADMINISTRATIVE INFORMATION

Protocol History

Version Number	Version Date	Summary of Revisions Made:
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible] "Presentation within 24 hours of symptom onset (or last seen well)" to "Presentation within 48 hours of symptom onset (or last seen well)"; [illegible] [illegible] following criteria: a) NIHSS ≥ [illegible] 7 [illegible] Adding 'secondary to antiplatelet treatment' into the exclusion [illegible] [illegible] [illegible] [illegible] [illegible] neurological severity (NIHSS <15 vs≥15), and haematoma [illegible] Updating the randomization to 'double [illegible] will commence within 48 hours'; [illegible]

Trial/Study Registration

[illegible]

Funding

[illegible]

Study Management & Oversight

[illegible]

Steering Committee (SC): [illegible]

Central Coordinating Centre (CCC): [illegible] *Responsibilities:* [illegible]

2. LIST OF ARREVIATIONS AND TERMS

□□□	□
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[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]

3. PROTOCOL SYNOPSIS

Co-Sponsors: [illegible]	**Trial Registration:** [illegible]
Title: [illegible]	
Study Duration [illegible]	**Clinical Phase** [illegible]
Objective: [illegible]	
Number of Participants: [illegible]	
Study Design: [illegible]	
Inclusion Criteria: [illegible]	
Exclusion Criteria: [illegible] **NOT** [illegible]	

Randomisation and study intervention: [illegible]
Outcome Measures _Primary outcome_: *Utility-weighted modified Rankin scale* [illegible] _Secondary outcomes:_ [illegible]

4. BACKGROUND AND RATIONALE

4.1 Heavy Burden of ICH

[illegible]

[illegible]

[illegible]

4.2 Chinese Herbal Medicine for ICH Treatment

[illegible]

4.3 Chinese Herbal Medicine FYTF-919 and Underlying Mechanisms

[illegible] **(Table 1)** [illegible]

[illegible]

Elements	Effect mechanism
R[illegible]	[illegible]
[illegible]	M[illegible]
R[illegible]	M[illegible]
R[illegible]	M[illegible]

[illegible]

[illegible] 1β, IL[illegible]α [23]. [illegible]

[illegible]κB signaling pathways by reducing TLR4 levels on microglia surrounding haematoma, [illegible] [illegible]κB signaling pathway such that it has a neuroprotective role [25]. As an [illegible]

4.4 Previous Clinical Trials on Chinese Herbal Medicine FYTF-919

[illegible]

4.5 Summary

[illegible]

5. AIMS AND OBJECTIVES

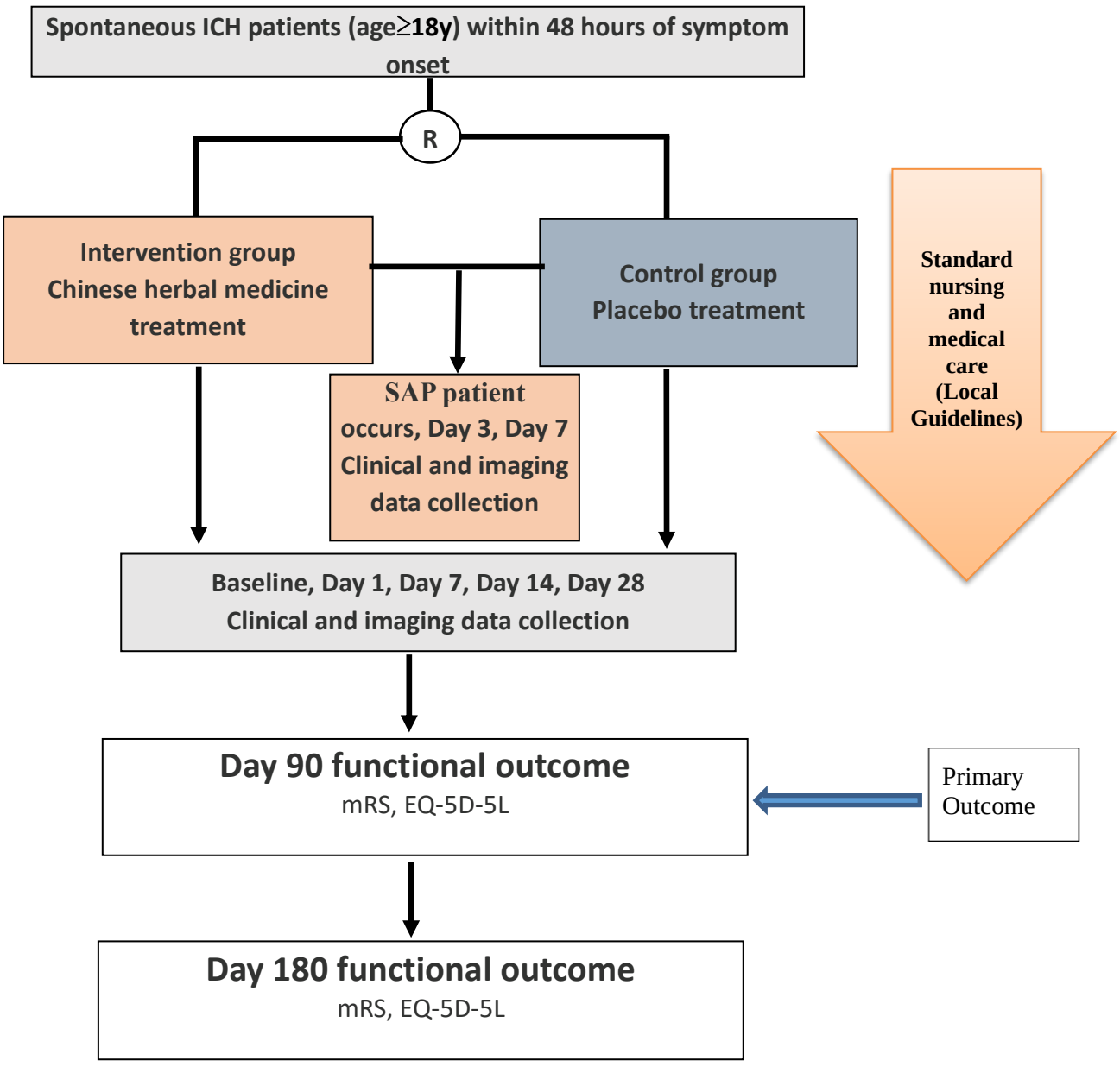
Primary aim

[illegible]

Secondary aims

6. METHODS

6.1 Overall Design


Spontaneous ICH patients (age≥18y) within 48 hours of symptom onset
R
Intervention group
Chinese herbal medicine treatment
Control group
Placebo treatment
Standard nursing and medical care (Local Guidelines)
SAP patient occurs, Day 3, Day 7
Clinical and imaging data collection
Baseline, Day 1, Day 7, Day 14, Day 28
Clinical and imaging data collection
Day 90 functional outcome
mRS, EQ-5D-5L
Primary Outcome
Day 180 functional outcome
mRS, EQ-5D-5L

6.2 Inclusion Criteria

[illegible]

[illegible] Age ≥18 years; [illegible]

[illegible] D[illegible]

[illegible]

[illegible] Meet severity criteria of either (a) NIHSS ≥[illegible] 7[illegible]

[illegible]

6.3 Exclusion Criteria

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

6.4 Ethical Issues

6.4.1 Institutional Ethics Committee Approval

[illegible]

6.4.2 Consent

A consent process

Patient consent process after presenting at hospital:

Surrogate consent: confusion, the patient's "surrogate" will be approached and will be provided with the ICF to read and act on the patient's behalf. Under the Guardianship Act of 1987 in Australia, a "person responsible" is the legally appointed guardian, their spouse or

to obtain the patient's consent will be documented, dated, and signed in the patient's file.

Withdrawal of consent **:** [illegible]

[illegible] the patient's file. Withdraw cons[illegible]

- [illegible]
- [illegible]
- [illegible]
- [illegible]

6.4.3 Confidentiality and Privacy

[illegible]

6.5 Study Site Selection, Participation and Responsibilities of Staff

Site eligibility criteria: [illegible]

- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
  - [illegible]
  - collect data on patients' stay in hospital,
  - [illegible]
  - [illegible]

Responsibilities of the site PI [illegible]

- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]

- [illegible]
- [illegible]
- Record and report all SAEs during 3 months' follow [illegible]

[illegible]

Hospital organisational questionnaire (HOQ): [illegible]

6.6 Randomisation

[illegible]

6.7 Intervention

Time to initiation of Chinese herbal medicine FYTF-919 or placebo: *The intervention after the randomization should be performed as soon as possible.*

Treatment duration: *28 days*

Intervention Group (Chinese herbal medicine treatment):

Control Group (Placebo treatment):

Discontinuation of the intervention

c. The investigator feels it is in the subject's best interest.

6.8 Outcome Measures

6.8.1 Primary Outcome

6.8.2 Secondary Outcomes

6.8.3 Safety Outcomes

AESI

Any other SAEs

6.9 Data Collection and Follow-up

All patients will be analysed according to the “intention to treat” principle. Data

6.9.1 Screening and Enrolment log

Screening and Enrolment

log. The log will record patient’s gender, initials, date and time of hospital arrival, date

and consent obtained and patient’s ineligibility. This form is also used as the

6.9.2 Patient Contact Details log

[illegible]

6.9.3 Information Collected at Each Stage

[illegible]

Baseline

[illegible]

- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]

Day 1

[illegible]

- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]

Day 7

[illegible]

- [illegible]

- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]

Day 14

[illegible]

- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]

Day 28

[illegible]

- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]

[illegible]

90-day Follow-up Blinded Assessment

Standardisation of outcome assessment: [illegible]

[illegible]

- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]

180-day Follow-up Blinded Assessment

[illegible]

- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]

Stroke related pneumonia (SAP)

[illegible]

- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]

- [illegible]
- [illegible]

Death

[illegible]

7. SAFETY

7.1 Data and Safety Monitoring Board (DSMB)

[illegible] *Responsibilities* [illegible]

- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]

7.2 Serious Adverse Events (SAEs)

[illegible]

- [illegible]

Recording and reporting

PI's opinion on the causal relationship to the randomised management group and t

definitions, the PI's opinion on the causal relationship to Chinese herbal medicine

8. QUALITY ASSURANCE

8.1 Monitoring of Sites

8.2 Collection and Storage of Essential Documents

- the PI's up

9. HEALTH ECONOMIC EVALUATION

healthcare payer's perspective. A range of sensitivity analyses (SA) includ

10. DATA MANAGEMENT

11. STATISTICAL CONSIDERATIONS

The sample of 1504 patients would give 90% power (α 0.05) to detect a difference

12. PUBLICATIONS, REPORTS AND DATA SHARING

the study to be published in the name of “CHAIN Investigators” with credit assigned

13. FUNDING

□

14. TIMELINES

Main study timelines	2021	2022	2023	2024	2025
Protocol design and documents development	→				
Site screening and selecting	→				
Central Ethics and HGRA application	→				
Sign contract with other investigators	→				
Site initiation	→				
Recruitment and commence intervention	→	→	→		
Outcome assessment	→	→	→		
Data clean and close out				→	
Analysis and Results				→	
Main study results publish					

□ □

15. REFERENCES

[illegible]

[1] 卢明,黄燕,杜宝新,梁伟雄,黄培新,刘茂才.中大量脑出血患者中西医结合救治后并发症及其死亡原因分析[J].中国中西医结合急救杂志,

[2] 陈婷婷,任晋婷,任丽娜,贺忠延,孙畅,王冬慧,孙明广,王芳,谢颖桢.中风急性期中经络与中脏腑痰热腑实证临床特点对比研究[J].北京中医药大学学报,

[3] [illegible]

[4] [illegible]

[5] [illegible]

[6] [illegible]

[7] [illegible]

[illegible]

[illegible] 张晓云 [illegible] 金伟 [illegible] 陈绍宏 [illegible] 复元醒脑法对 [illegible] 例急性脑出血临床验证观察 [illegible] 辽宁中医杂志 [illegible]

[illegible] 陈绍宏 [illegible] 张晓云 [illegible] 中风醒脑口服液治疗急性脑出血临床研究 [illegible] 中国中医急症 [illegible]

[illegible] 李艳青 [illegible] 益气活血、泄热熄风法治疗出血性中风急性期的临床验证研究 [illegible] 成都中医药大学 [illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

Chinese Herbal medicine in Acute INtracerebral haemorrhage (CHAIN) trial

Statistical Analysis Plan (SAP)

Version: 1.0 (Final)

Date: 11 January 2024

Authors:
Qiang Li, Lili Song, Laurent Billot, Yang Zhao, Rustam AI-Shahi Salman, Graeme Hankey, Craig S. Anderson, Jianwen Guo, on behalf of the CHAIN Investigators

Corresponding author:
Qiang Li
The George Institute for Global Health
Faculty of Medicine and Health, UNSW, Sydney, Australia
qli@georgeinstitute.org

Table of Contents

1 Administrative information

1.1 Study identifiers

- Protocol Number: Version: 4.0, Date: 14 September 2022
- ClinicalTrials.gov register Identifier: NCT05066620

1.1 Revision history

Version	Date	Details
0.1 (draft)	05 October 2023	First draft by Q Li
0.2 (revision)	02 November 2023	Reviewed by C Anderson and L Song
0.3 (revision)	16 November 2023	Reviewed by R Salman and G Hankey
0.4 (revision)	04 December 2023	Reviewed by L Song
1.0 (Final)	18 December 2023	Reviewed by R Salman, G Hankey and L Billot
1.0 (Final)	11 January 2024	Correction of minor comments by Q Li

1.2 Contributors to the statistical analysis plan

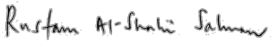
1.2.1 Roles and responsibilities

Name and ORCID	Affiliation	Role on study	SAP contribution
Qiang Li	The George Institute for Global Health, UNSW Sydney	Study statistician	Prepared initial draft and revisions
Lili Song	The George Institute for Global Health, UNSW, Sydney, Australia. The George Institute for Global Health, Beijing, China.	Program investigator	Reviewed and approved final version
Laurent Billot	The George Institute for Global Health, UNSW Sydney	Senior adviser of statistical analysis	Contributed to methodology, revision of the first draft, and review and approval of the final version
Yang Zhao	The George Institute for Global Health, UNSW, Sydney, Australia. The George Institute for Global Health, Beijing, China.	Researcher	Reviewed and approved final version
Rustam Al-Shahi Salman	Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh. UK	International expert	Contributed to methodology, revision of the first draft, and review and approval of the final version

Name and ORCID	Affiliation	Role on study	SAP contribution
Graeme J. Hankey	Medical School, The University of Western Australia, Perth, Australia; The Perron Institute for Neurological and Translational Science, Perth, Australia.	International expert	Contributed to methodology, revision of the first draft, and review and approval of the final version
Craig Anderson	The George Institute for Global Health, UNSW Sydney	Co-principal investigator	Reviewed and approved all versions
Jianwen Guo	The Second Affiliated Hospital of Chinese Medicine, Guangdong, China	Co-principal investigator	Reviewed and approved all versions

1.2.2 Approvals

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) topic E9 Statistical Principles for Clinical Trials. In particular, we confirm that this analysis plan was developed in a completely blinded manner, that is without knowledge of the effect of the intervention(s) being assessed.

Name	Signature	Date
Qiang Li		17 January 2024
Lili Song		
Laurent Billot		17 January 2024
Yang Zhao		
Rustam AI-Shahi Salman		15 January 2024
Graeme J. Hankey		JANUARY 15, 2024
Craig S. Anderson		
Jianwen Guo		

2 Abbreviations

BP	Blood pressure
BI	Barthel index
CACE	Complier Average Cause Effect
CCB	Calcium channel blocker
CCC	Central coordinating centre
CHAIN	Chinese Herbal medicine in Acute INtracerebral haemorrhage
CI	Confidence interval
CPIS	Clinical pulmonary infection score
CRF	Case reports form
CT	Computerised tomography
DSMB	Data and safety monitoring board
EDC	Electronic data collection
EQ-5D	EuroQoL Group 5-dimension self-report questionnaire
GCS	Glasgow coma scale
HR	Heart rate
HRQoL	Health-related quality of life
IC	Informed consent
ICF	Inform consent form
ICH	Intracerebral haemorrhage
mRS	Modified Rankin scale
NIHSS	National Institute of Health Stroke Scale
PI	Principal investigator
PIS	Patient information sheet
ICF	Patient information sheet and inform consent form
RCC	Regional coordinating centre
RCTs	Randomised Controlled Trials
SAE	Serious adverse event
SAP	Stroke-associated pneumonia
SC	Steering committee
SD	Standard deviation
SOP	Standard operation process
TCM	Traditional Chinese medicine
TGI CHINA	The George Institute for Global Health, China; Or the George Institute for Global Health (Australia), Beijing representative office
UW-mRS	Utility-weighted modified Rankin scale

3 Introduction

3.1 Study synopsis

CHAIN is an investigator initiated and conducted, multicenter, prospective, randomised, double-blind placebo-controlled trial that aims to determine the efficacy and safety of FYTF-919 in patients with acute intracerebral haemorrhage (ICH) at hospitals in China. The full protocol was published in the journal Cerebrovascular Diseases in October 2023 [1].

3.2 Study population

A total of 1504 patients with diagnosis of ICH are to be recruited from approximately 20-30 hospitals in China.

3.2.1 Inclusion criteria

- Age ≥18 years;
- Diagnosis of spontaneous ICH, confirmed by brain imaging;
- Presentation within 48 hours of symptom onset (or last seen well);
- Meet severity criteria of either (a) NIHSS ≥8, or (b) GCS ≤14;
- Provide written informed consent by patient (or approved surrogate).

3.2.2 Exclusion criteria

- ICH secondary to a structural abnormality in the brain (e.g. cerebrovascular malformation, arterial aneurysm, tumour, Moyamoya disease, trauma, or previous ischemic stroke), or secondary to cerebral amyloid angiopathy, or secondary to reperfusion treatment for ischemic stroke, or secondary to anticoagulant treatment, or secondary to antiplatelet treatment;
- Unlikely to potentially benefit from therapy (e.g. advanced dementia) or judged by responsible treating clinician to have a high likelihood of early death irrespective of treatment;
- Other medical illness that will interfere with outcome assessments and follow-up (e.g. known significant pre-stroke disability [mRS scores 3-5], advanced cancer and renal failure);
- Known definite contraindication to the Chinese herbal medicine;
- Women who are known to be pregnant or lactating;
- Currently participating in another trial which would interfere with outcome assessments.

3.3 Study interventions

3.3.1 Randomisation

After patient eligibility is confirmed, randomisation is via a central internet-based system according to a block grouping method stratified by site, neurological severity (NIHSS scores <15 vs. ≥15), and haematoma location (basal ganglia or lobe vs. thalamus or cerebellum or brain stem or ventricle) to ensure these key prognostic factors are balanced between groups. Location of ventricle here is referring to pure intraventricular haemorrhage.

3.3.2 Study treatment

The first dose of either active drug or matching placebo is given as soon as possible after randomisation. This is as an oral liquid 33 ml t.i.d. × 28 days (NB: for patients who are unconscious or have dysphagia, a dose of 25 ml * Q.6.H is given via nasogastric tube).

FYTF-919 (*active treatment*) group: The FYTF-919 (ZFXN prescription) is in accordance with Chinese good manufacture practice of medical products standards (GMP). As a type of plant compound, FYTF-919 is composed mainly of Renshen (Panax ginseng), Dahuang (Radix et Rhizoma Rhei), Sanqi (Radix Notoginseng), and Chuanxiong (Rhizoma Ligustici Chuanxiong), with sorbic acid and polysorbate 80 as auxiliary materials.

Control (*placebo treatment*) group: The placebo is a plant-flavored solution, composed mainly of soybean peptide and black sugar syrup combined with an edible essence and maltodextrin, salt and monosodium glutamate as auxiliary materials, and it has no biologic activity.

3.4 Outcomes

3.4.1 Primary outcome

Utility-weighted modified Rankin scale (UW-mRS) at 90 days [6].

The algorithm of UW-mRS is illustrated below using ICH population from previous publication [6]:

UW-mRS
- = 0.97 if mRS=0
- = 0.88 if mRS=1
- = 0.74 if mRS=2
- = 0.55 if mRS=3
- = 0.20 if mRS=4
- = -0.19 if mRS=5
- = 0 if mRS=6

3.4.2 Secondary outcomes

- UW-mRS at 180 days;
- An ordinal analysis of the mRS at 28, 90 and 180 days;
- Death or disability, defined as mRS scores 4-6 at 28, 90 and 180 days;
- Death at 28, 90 and 180 days;
- Major disability (mRS 4-5) at 28, 90 and 180 days;
- Health-related quality of life on the EuroQoL EQ-5D-5L [10] measure at 28, 90 and 180 days;
- Basic activities of daily living according to the Barthel index (BI) at 28, 90 and 180 days;
- NIHSS at 24 hours and 7 days;
- Haematoma volume and cerebral oedema volume at 24 hours, 7 days, 14 days (or hospital discharge, if sooner);
- The stroke-associated pneumonia (SAP) by day 7 during follow-up;
- Clinical pulmonary infection score (CPIS) on days 0, 3 and 7 after stroke-associated pneumonia (SAP)

3.4.3 Safety

- Serious adverse events (SAEs) during follow-up
- Adverse events of special interest (AESI) during follow-up, including haematoma enlargement (>6 ml or 33%), new intracranial haematoma and diarrhoea.

4 Analysis principles

4.1 Sample size

The sample of 1504 patients provides 90% power (α 0.05) to detect a difference in average scores for UW-mRS between the active and placebo groups of 0.06 (i.e., 0.59 vs. 0.65; SD = 0.32), assuming equal group participations, 6% non-adherence rate, and 10% lost to follow-up. The calculation was based on data from the second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) where the mean UW-mRS was estimated as 0.59 in control 'less intensive BP control' group [2].

4.2 Software

Analyses will be conducted primarily using SAS 9.4 on SAS Enterprise Guide (version 8.3 or above).

4.3 Interim analyses

Two formal interim analyses were undertaken after 500 and 1000 patients who had completed 90-day follow-up to review the data related to treatment efficacy, participant safety and quality of trial conduct using a Haybittle-Peto stopping rule for efficacy [3]. Given the conservative rule used and the negligible amount of type-I error rate spent at the interim analysis, the significance threshold will remain at 5% for the final analysis.

4.4 Multiplicity adjustment

Statistical tests are to be two-sided with a nominal level of α set at 5%. Analysis of the primary outcome (UW-mRS at 90 days) will not be adjusted for multiplicity. For other secondary outcomes measured in all stroke patients (i.e. ordered mRS, death or major disability, NIHSS and HRQoL at different timepoints), we will control the family-wise error rate by applying a sequential Holm-Sidak correction [4]. Briefly, the approach consists of ordering all p-values from smallest to largest, and then comparing them to an adjusted level of significance calculated as $1-(1-0.05)^{1/C}$, where C indicates the number of comparisons that remain. The sequential testing procedure stops as soon as a p value fails to reach the corrected significance level. This will apply only to the primary analysis of an outcome (i.e. not to sensitivity analyses). For HRQoL, it will only apply to the analysis of the overall utility score. For clinical pulmonary infection score, it will only apply to the analysis of any stroke-associated pneumonia (SAP). For each secondary outcome only the primary time point is chosen to be adjusted for multiplicity, for example outcomes at day 90 will be used except that NIHSS and SAP are at day 7 (see Table 10). No multiplicity adjustment will be applied to safety outcomes.

4.5 Data sets analysed

4.5.1 Analysis populations

We will use 2 analysis populations:

- The ***intention-to-treat (ITT) population*** is defined as all patients who were randomised, regardless of their diagnosis or adherence to the study treatment protocol. This population includes individuals who did not withdraw their consent for the use of their data. *The ITT population will serve as the primary analysis set for all analyses*.
- The ***per-protocol (PP) population*** is defined as all patients from the ITT population excluding patients who had a relevant protocol violation defined as any of the following:
  - Age <18 years

- Randomised >48 hours after stroke onset
- NIHSS <8 and GCS 15
- Final diagnosis was not spontaneous ICH
- Patients who were found later in the trial to have received incorrect treatment or incorrect dose of the allocated study drug after confirmation by local investigators.
- Other major protocol violations which have been adjudicated, for example concomitant TCM contains same components of FYTF-919.

4.5.2 Analysis strategy

For all outcomes, complete case analyses will be performed on the ITT population. Adjusted analyses and sensitivity analyses will be conducted on the PP population for the primary outcome only. A CACE analysis will be considered in a secondary analysis if necessary, for example more than 20% of subjects have dropped-in and dropped-out of treatment groups.

As the data collection for outcomes at 180 days will not be completed by the time of database lock, the treatment effects on secondary outcomes at 180 days will be analysed separately in a secondary analysis.

5 Planned analyses

4.1 Subject disposition

The flow of patients through the trial will be displayed in a Consolidated Standards of Reporting Trials (CONSORT) [5] diagram (see Figure 1). The report will include: the number of screened patients who met study the inclusion criteria and the number of patients included, and reasons for exclusion of non-included patients.

5.1 Patient characteristics and baseline comparisons

Baseline characteristics will be 10summarized by treatment groups (see Table 1). Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Continuous variables will be summarised using mean and SD, and median and interquartile range (Q1-Q3). No statistical test will be performed on baseline characteristics.

5.2 Concomitant therapies and treatment of stroke

All assessments performed and interventions received between Day 1, 7, 14 and 28 will be described by treatment group. No formal statistical tests are planned for these variables.

5.3 Adherence to study intervention

Duration of study treatment will be summarised in days between treatment groups. Categorical variable of treatment duration, 1-7 days, 8-14 days, 15-21 days and 22 days or more will be also analysed in case of any outlies in treatment duration. The number of completed bottles will be also summarised between treatment groups. Adequate adherence will be described and is defined as more than or equal 80% of study drug have been taken.

5.4 Analysis of the primary outcome

The primary outcome of UW-mRS at 90 days will be calculated from mRS and EQ-5D scores using an algorithm illustrated in our previous publication [6]. For the primary outcome, a general linear regression will be performed to analyse whether FYTF-919 is superior to placebo. Raw mean and SD of UW-mRS and mean difference and 95%CI between the treatment groups will be provided.

5.4.1 Main analysis

The main analysis will be performed in the ITT population using general linear regression with UW-mRS collected at Day 90 as the dependent variable. Treatment allocation will be included as a fixed categorical effect. To account for the stratification variables and to maximise precision [7], site [8], baseline NIHSS score (<15 vs ≥15) and haematoma location (basal ganglia or cerebral lobe vs thalamus or cerebellum or brainstem or ventricle) will also be included as fixed effects. The effect of the intervention will be presented as mean difference and its 95% confidence interval (CI), using the placebo arm as the reference.

5.4.2 Adjusted analyses

Adjusted analyses will be performed by adding the following covariates to the main linear regression model: age (continuous), mRS before stroke (categorical), sex (male vs female), time to randomisation (<12 vs ≥12 hours). The adjusted treatment effect will be reported as the adjusted mean difference and 95% CI. Adjusted analyses will also be performed in the PP analysis dataset.

5.4.3 Subgroup analyses

Six pre-specified subgroup analyses will be carried out, irrespective of whether there is a significant treatment effect on the primary outcome. These subgroup analyses will only be performed in the ITT population.

Pre-randomisation subgroups are defined as follows:

- Age (<65 vs ≥65 years)
- Sex (male vs female)
- Time to randomisation (<12 vs ≥12 hours)
- Baseline NIHSS score (<15 vs ≥15)
- Baseline haematoma volume (<15 vs ≥15 ml))
- Haematoma location (basal ganglia or cerebral lobe vs thalamus or cerebellum or brainstem or ventricle)

The analysis for each subgroup will be performed by adding the subgroup variable as well as its interaction with the intervention as fixed effects to the main linear regression model. Within each subgroup, summary measures will include raw mean and SD within each treatment arm, as well as the mean difference for treatment effect with a 95% CI. The results will also be displayed on a forest plot, including estimated mean, SE and the p-value for heterogeneity corresponding to the interaction term between the intervention and subgroup variable.

5.4.4 Treatment of missing data

The proportion of data missing for the primary outcome (UW-mRS at 90 days) will be described while blinded to the intervention. In case of non-negligible amounts of missing data (>5%), we will use multiple imputations by chained equation to assess the impact of missing data to the results. We will run an imputation model under the missing at random (MAR) assumption. This MAR imputation model will use fully conditional specification (FCS) [9] and will include the following variables: mRS at 28 days and 90 days, HRQoL EQ-5D-5L utility score at 28 days and 90 days, the NIHSS at 24 hours and 7 days (or hospital discharge, if sooner), a

variable indicating the intervention, and all key socio-demographic, clinical, and medical baseline variables. The mRS will be imputed using an ordinal logistic model. Other variables will be imputed using either linear regression (for continuous/ordinal variables) or a discriminant function method (for nominal variables). One hundred sets of imputed data will be created. Once mRS is imputed, UW-mRS will be calculated using same algorithm and analysed using the model described in section 5.4.1. 100 imputed datasets will be produced and estimates of the treatment effect and its standard errors will be combined to obtain a pooled common mean difference and 95%CI.

Multiple imputations will only be applied to the ITT analysis.

5.4.5 Per-protocol analyses

The main model (section 5.4.1) as well as the adjusted analyses (section 5.4.2) will be repeated in the PP population as defined in Section 4.5.1.

Protocol deviations will be categorised and reported as the number and proportion of subjects experiencing a deviation. A listing of all protocol deviations will be provided.

5.4.6 Other sensitivity analyses

In principal, we will utilize the HRQoL EQ-5D-5L utility score at day 90 to calculate the UW-mRS score. To achieve this, we will use an ordinary least squares regression model, with mRS scores serving as a categorical explanatory variable, and EQ-5D-5L utility scores as the continuous dependent variable. The model will generate beta-coefficients, which will be utilized as the weights for the UW-mRS score.

There are several reasons for not using in-study HRQoL utility scores in the primary analysis. First and foremost, approximately 15%-20% of HRQoL data at day 90 is missing, as indicated by a blinded review from the DSMB report. Secondly, the utility weights derived from previous large ICH population studies [6] are deemed more suitable and applicable.

The following section outlines three sensitivity analyses to be conducted:

In the first sensitivity analysis, we will utilize the available HRQoL EQ-5D-5L utility scores at day 90 to derive utility weights. These weights will be used to impute utility values for individuals with missing utility scores at day 90, and we will then repeat the primary analysis within the ITT population.

The second sensitivity analysis involves using available HRQoL EQ-5D-5L utility scores at day 90 to derive utility weights, which is the same as the first sensitivity analysis for this step This analysis will be then repeated specifically within the subset of subjects with non-missing HRQoL data.

In the third sensitivity analysis, in case of subjects who had missing HRQoL EQ-5D-5L utility score at day 90 but had been followed up more than 180 days with available HRQoL EQ-5D-5L utility scores , we will impute utility values at day 90 using data at day 180. Then, these imputed values will be used to derive utility weights for the UW-mRS score, which will then be applied to the entire ITT population. Subsequently, we will repeat the primary analysis.

5.5 Analysis of secondary outcomes

All secondary outcome analyses described in this section will be performed in the ITT (primary) and PP (sensitivity) analyses sets as defined in Section 4.5.1

5.5.1 UW-mRS at 180 days

The data collection of the UW-mRS at 180 days will not be completed by the time of database lock and will be analysed separately in secondary analysis. Exploratory analysis using repeated measurement of UW-mRS by day 28, 90 and 180 will be conducted and reported in a secondary publication and is not described in this SAP.

5.5.2 Ordinal analyses of mRS

The outcome of the mRS at 28 and 90 days will be analysed separately as an ordinal variable with 7 levels. The intervention effect will be estimated as the OR of a higher mRS between the active arm and the placebo arm obtained from an ordinal logistic model. The effect of the intervention will be presented as the OR of a worse outcome and its 95% confidence interval (CI) using the placebo arm as the reference (i.e., where an OR greater than unity corresponds to an increase in mRS in the active arm compared to the placebo arm). We will also apply the covariate adjustments described in Section 5.4.2 but no subgroup or imputed analysis will be performed on this outcome.

We will assess the proportional-odds assumption using a score test. If a violation is detected, we will proceed with the analysis and interpret the intervention OR as an average effect across all mRS levels, recognizing that it may not remain constant across all levels. This assessment will be complemented by a graphical analysis of shifts across categories using bar plots.

5.5.3 Binary analyses of mRS

A binary analysis of the mRS at 28 and 90 days will be performed by dichotomising the mRS as either 'poor' (scores 4-6) or 'favourable' (scores 0-3) outcomes. This analysis will be conducted using logistic regression. The effect of FYTF-919 will be presented as the OR of a poor outcome with associated 95% CI. We will also apply the covariate adjustments described in Section 5.4.2 but no subgroup or imputed analysis will be performed on this outcome. A similar analysis will be performed on mortality alone (mRS of 6 vs 0-5) and on disability alone (mRS 4-5 vs 0-3). For disability alone, the analysis will be restricted to subjects who are alive at corresponding timepoints (mRS 0-5).

5.5.4 Health related quality of life – EQ-5D-5L

At day 28 and day 90, each of the 5 EQ-5D dimensions will be summarised in percentages between treatment groups and no statistical test will be performed. The visual analogous scale (score of 0 to 100) will be analysed using linear regression and the overall health utility EQ-5D-5L score will be calculated using Chinese norm [10] and compared between groups in a similar manner to that used for the visual analogous scale.
For patients who died before the planed timepoints, the EQ-5D-5L utility score will be imputed as zero. Both survivors and all subjects including deaths will be analysed separately within ITT population. We do not plan to undertake adjusted or subgroup analyses.

5.5.5 Basic activity of daily living according to the Barthel Index (BI)

The Barthel Index (BI) at 28 and 90 days will be analysed as a continuous outcome using linear regression same as the primary outcome, but no subgroup or imputed analysis will be performed on this outcome.

5.5.6 NIHSS score at 24 hours and 7 days

The NIHSS scores at 24 hours and at 7 days will be analysed as a continuous variable using an unadjusted linear regression model. The effect of FYTF-919 will be presented as the mean difference and associated 95%CI. The covariate adjustments described in Section 5.4.2 will also be applied but no subgroup or imputed analysis will be performed on this outcome.

5.5.7 Haematoma volume and cerebral oedema volume

Haematoma volumes and cerebral edema volumes at the time of presentation from initial image data reported from the investigator will be summarised using mean and SD, median and inter-quarter range (Q1, Q3). The mean difference and 95%CI will be estimated between treatment groups using t-test and the median difference and 95%CI will be estimated using log-linear regression assuming log-normal distribution of haemotoma volumes.

Haemotoma growth and edema analysis based on imaging data will be analysed and reported in a secondary publication and is not described in this SAP.

5.5.8 Clinical pulmonary infection score (CPIS) and Stroke-associated Pneumonia (SAP)

Clinical pulmonary infection score (CPIS) at baseline, day 3 and day 7 will be summarised as mean and SD between active arm and placebo arm. Any stroke-associated pneumonia (SAP) during follow-up will be summarised as the proportions and analysis will be conducted using logistic regression, same analysis method as binary mRS in section 5.5.3. Analysis will be conducted within the ITT population, and we do not have plans to perform adjusted or subgroup analyses.

5.6 Analysis of other outcomes

5.6.1 Serious adverse events (SAEs) and deaths

SAEs will be summarised as the number of events as well as the number and proportion of patients experiencing at least one SAE event. The overall proportion of patients with SAEs in the intervention and control arms will be compared using logistic regression, as in the binary analysis of mRS (see Section 5.5.1). Additionally, Adverse Events of Special Interest (AESI) reported by the local investigators, including hematoma enlargement (>6mL or 33%), new intracranial hematoma and diarrhea will be summarised by treatment groups. Primary and underlying causes of deaths will be summarised by treatment arm with no formal test.

A listing of all SAEs will be compiled (in an appendix).

5 References

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Appendix 1: Proposed Tables and figures

1.1 Tables

Table 1. Baseline characteristics

	Active drug (N =)	Placebo drug (N =)	Total (N =)
Age (years)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Sex	xxx	xxx	xxx
Male	xxx xx.x%	xxx xx.x%	xxx xx.x%
Female	xxx xx.x%	xxx xx.x%	xxx xx.x%
Ethnicity	xxx	xxx	xxx
Han	xxx xx.x%	xxx xx.x%	xxx xx.x%
Non-Han Minorities	xxx xx.x%	xxx xx.x%	xxx xx.x%
Height (cm)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Weight (kg)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
BMI (kg/m^2)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Current smoking	xxx	xxx	xxx
No	xxx xx.x%	xxx xx.x%	xxx xx.x%
Yes	xxx xx.x%	xxx xx.x%	xxx xx.x%

	Active drug (N =)	Placebo drug (N =)	Total (N =)
Current drinking	xxx	xxx	xxx
No	xxx xx.x%	xxx xx.x%	xxx xx.x%
Yes	xxx xx.x%	xxx xx.x%	xxx xx.x%
Systolic Blood Pressure on arrival (mmHg)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Diastolic Blood Pressure on arrival (mmHg)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Heart Rate on arrival (bpm)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Respiratory rate on arrival	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
First GCS on arrival	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
First NIHSS on arrival	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
NIHSS category	xxx	xxx	xxx
NIHSS <15	xxx xx.x%	xxx xx.x%	xxx xx.x%
NIHSS >=15	xxx xx.x%	xxx xx.x%	xxx xx.x%

	Active drug (N =)	Placebo drug (N =)	Total (N =)
Largest hematoma location	xxx	xxx	xxx
Basal ganglia	xxx xx.x%	xxx xx.x%	xxx xx.x%
Lobe	xxx xx.x%	xxx xx.x%	xxx xx.x%
Thalamus	xxx xx.x%	xxx xx.x%	xxx xx.x%
Cerebellar	xxx xx.x%	xxx xx.x%	xxx xx.x%
Brain stem	xxx xx.x%	xxx xx.x%	xxx xx.x%
Brain ventricle	xxx xx.x%	xxx xx.x%	xxx xx.x%
Time from onset to arrival (hours)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Time from onset to randomisation (hours)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Medical history	xxx	xxx	xxx
Previous Hypertension	xxx xx.x%	xxx xx.x%	xxx xx.x%
Previous Diabetes Mellitus	xxx xx.x%	xxx xx.x%	xxx xx.x%
Previous Hyperlipidemia	xxx xx.x%	xxx xx.x%	xxx xx.x%
Previous Coronary Heart Disease	xxx xx.x%	xxx xx.x%	xxx xx.x%
Previous Atrial fibrillation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Any anticoagulant treatment	xxx xx.x%	xxx xx.x%	xxx xx.x%
Any antiplatelet treatment	xxx xx.x%	xxx xx.x%	xxx xx.x%

Table 2. Stroke treatment and therapy other than investigation medication

Medication/ Therapy Visits	Active drug (N =)	Placebo drug (N =)	Total (N =)
Adjunctive therapy			
Baseline	xxx	xxx	xxx
ICU	xxx xx.x%	xxx xx.x%	xxx xx.x%
Surgery	xxx xx.x%	xxx xx.x%	xxx xx.x%
Tracheal Intubation Tracheotomy	xxx xx.x%	xxx xx.x%	xxx xx.x%
Mechanical Ventilation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Physical or drug hypothermia	xxx xx.x%	xxx xx.x%	xxx xx.x%
Nasal Feeding	xxx xx.x%	xxx xx.x%	xxx xx.x%
Urinary Catheter	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other Invasive treatment	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other treatments:			
Lower body temperature	xxx xx.x%	xxx xx.x%	xxx xx.x%
Analgesia and sedation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Proton pump inhibitors	xxx xx.x%	xxx xx.x%	xxx xx.x%
Diuretics	xxx xx.x%	xxx xx.x%	xxx xx.x%
Anti-epilepsy	xxx xx.x%	xxx xx.x%	xxx xx.x%
Dehydration	xxx xx.x%	xxx xx.x%	xxx xx.x%
BP control	xxx xx.x%	xxx xx.x%	xxx xx.x%
Glucose control	xxx xx.x%	xxx xx.x%	xxx xx.x%
BP elevating	xxx xx.x%	xxx xx.x%	xxx xx.x%
Anticoagulation invert	xxx xx.x%	xxx xx.x%	xxx xx.x%
Rehabilitation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Acupuncture	xxx xx.x%	xxx xx.x%	xxx xx.x%
24h (± 3h)	xxx	xxx	xxx
ICU	xxx xx.x%	xxx xx.x%	xxx xx.x%
Surgery	xxx xx.x%	xxx xx.x%	xxx xx.x%
Tracheal Intubation Tracheotomy	xxx xx.x%	xxx xx.x%	xxx xx.x%
Mechanical Ventilation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Physical or drug hypothermia	xxx xx.x%	xxx xx.x%	xxx xx.x%
Nasal Feeding	xxx xx.x%	xxx xx.x%	xxx xx.x%
Urinary Catheter	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other Invasive treatment	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other treatments:			
Lower body temperature	xxx xx.x%	xxx xx.x%	xxx xx.x%
Analgesia and sedation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Proton pump inhibitors	xxx xx.x%	xxx xx.x%	xxx xx.x%

Diuretics	xxx xx.x%	xxx xx.x%	xxx xx.x%
Anti-epilepsy	xxx xx.x%	xxx xx.x%	xxx xx.x%
Dehydration	xxx xx.x%	xxx xx.x%	xxx xx.x%
BP control	xxx xx.x%	xxx xx.x%	xxx xx.x%
Glucose control	xxx xx.x%	xxx xx.x%	xxx xx.x%
BP elevating	xxx xx.x%	xxx xx.x%	xxx xx.x%
Anticoagulation invert	xxx xx.x%	xxx xx.x%	xxx xx.x%
Rehabilitation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Acupuncture	xxx xx.x%	xxx xx.x%	xxx xx.x%
Day7 (± 1day)	xxx	xxx	xxx
ICU	xxx xx.x%	xxx xx.x%	xxx xx.x%
Surgery	xxx xx.x%	xxx xx.x%	xxx xx.x%
Tracheal Intubation Tracheotomy	xxx xx.x%	xxx xx.x%	xxx xx.x%
Mechanical Ventilation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Physical or drug hypothermia	xxx xx.x%	xxx xx.x%	xxx xx.x%
Nasal Feeding	xxx xx.x%	xxx xx.x%	xxx xx.x%
Urinary Catheter	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other Invasive treatment	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other treatments:			
Lower body temperature	xxx xx.x%	xxx xx.x%	xxx xx.x%
Analgesia and sedation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Proton pump inhibitors	xxx xx.x%	xxx xx.x%	xxx xx.x%
Diuretics	xxx xx.x%	xxx xx.x%	xxx xx.x%
Anti-epilepsy	xxx xx.x%	xxx xx.x%	xxx xx.x%
Dehydration	xxx xx.x%	xxx xx.x%	xxx xx.x%
BP control	xxx xx.x%	xxx xx.x%	xxx xx.x%
Glucose control	xxx xx.x%	xxx xx.x%	xxx xx.x%
BP elevating	xxx xx.x%	xxx xx.x%	xxx xx.x%
Anticoagulation invert	xxx xx.x%	xxx xx.x%	xxx xx.x%
Rehabilitation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Acupuncture	xxx xx.x%	xxx xx.x%	xxx xx.x%
Day 14 (± 2days)	xxx	xxx	xxx
ICU	xxx xx.x%	xxx xx.x%	xxx xx.x%
Surgery	xxx xx.x%	xxx xx.x%	xxx xx.x%
Tracheal Intubation Tracheotomy	xxx xx.x%	xxx xx.x%	xxx xx.x%
Mechanical Ventilation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Physical or drug hypothermia	xxx xx.x%	xxx xx.x%	xxx xx.x%
Nasal Feeding	xxx xx.x%	xxx xx.x%	xxx xx.x%
Urinary Catheter	xxx xx.x%	xxx xx.x%	xxx xx.x%

Other Invasive treatment	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other treatments:			
Lower body temperature	xxx xx.x%	xxx xx.x%	xxx xx.x%
Analgesia and sedation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Proton pump inhibitors	xxx xx.x%	xxx xx.x%	xxx xx.x%
Diuretics	xxx xx.x%	xxx xx.x%	xxx xx.x%
Anti-epilepsy	xxx xx.x%	xxx xx.x%	xxx xx.x%
Dehydration	xxx xx.x%	xxx xx.x%	xxx xx.x%
BP control	xxx xx.x%	xxx xx.x%	xxx xx.x%
Glucose control	xxx xx.x%	xxx xx.x%	xxx xx.x%
BP elevating	xxx xx.x%	xxx xx.x%	xxx xx.x%
Anticoagulation invert	xxx xx.x%	xxx xx.x%	xxx xx.x%
Rehabilitation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Acupuncture	xxx xx.x%	xxx xx.x%	xxx xx.x%
Day28 (± 3days)	xxx	xxx	xxx
ICU	xxx xx.x%	xxx xx.x%	xxx xx.x%
Surgery	xxx xx.x%	xxx xx.x%	xxx xx.x%
Tracheal Intubation Tracheotomy	xxx xx.x%	xxx xx.x%	xxx xx.x%
Mechanical Ventilation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Physical or drug hypothermia	xxx xx.x%	xxx xx.x%	xxx xx.x%
Nasal Feeding	xxx xx.x%	xxx xx.x%	xxx xx.x%
Urinary Catheter	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other Invasive treatment	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other treatments:			
Lower body temperature	xxx xx.x%	xxx xx.x%	xxx xx.x%
Analgesia and sedation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Proton pump inhibitors	xxx xx.x%	xxx xx.x%	xxx xx.x%
Diuretics	xxx xx.x%	xxx xx.x%	xxx xx.x%
Anti-epilepsy	xxx xx.x%	xxx xx.x%	xxx xx.x%
Dehydration	xxx xx.x%	xxx xx.x%	xxx xx.x%
BP control	xxx xx.x%	xxx xx.x%	xxx xx.x%
Glucose control	xxx xx.x%	xxx xx.x%	xxx xx.x%
BP elevating	xxx xx.x%	xxx xx.x%	xxx xx.x%
Anticoagulation reversal	xxx xx.x%	xxx xx.x%	xxx xx.x%
Rehabilitation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Acupuncture	xxx xx.x%	xxx xx.x%	xxx xx.x%

Table 3. Reported stroke complications by visits

Complications Visits	Active drug (N =)	Placebo drug (N =)	Total (N =)
Baseline	xxx	xxx	xxx
Infection (respiratory)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (urinary)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (digest)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (other)	xxx xx.x%	xxx xx.x%	xxx xx.x%
AKI	xxx xx.x%	xxx xx.x%	xxx xx.x%
Gastrointestinal bleeding	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hypertonic coma	xxx xx.x%	xxx xx.x%	xxx xx.x%
Pulmonary embolism	xxx xx.x%	xxx xx.x%	xxx xx.x%
Intracerebral hypertension/herniation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hydrocephalus	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hyperthermia	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other	xxx xx.x%	xxx xx.x%	xxx xx.x%
24h (± 3h)	xxx	xxx	xxx
Infection (respiratory)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (urinary)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (digest)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (other)	xxx xx.x%	xxx xx.x%	xxx xx.x%
AKI	xxx xx.x%	xxx xx.x%	xxx xx.x%
Gastrointestinal bleeding	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hypertonic coma	xxx xx.x%	xxx xx.x%	xxx xx.x%
Pulmonary embolism	xxx xx.x%	xxx xx.x%	xxx xx.x%
Intracerebral hypertension/herniation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hydrocephalus	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hyperthermia	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other	xxx xx.x%	xxx xx.x%	xxx xx.x%
Day7 (± 1day)	xxx	xxx	xxx
Infection (respiratory)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (urinary)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (digest)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (other)	xxx xx.x%	xxx xx.x%	xxx xx.x%
AKI	xxx xx.x%	xxx xx.x%	xxx xx.x%
Gastrointestinal bleeding	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hypertonic coma	xxx xx.x%	xxx xx.x%	xxx xx.x%
Pulmonary embolism	xxx xx.x%	xxx xx.x%	xxx xx.x%
Intracerebral hypertension/herniation	xxx xx.x%	xxx xx.x%	xxx xx.x%

Hydrocephalus	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hyperthermia	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other	xxx xx.x%	xxx xx.x%	xxx xx.x%
Day 14 (± 2days)	xxx	xxx	xxx
Infection (respiratory)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (urinary)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (digest)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (other)	xxx xx.x%	xxx xx.x%	xxx xx.x%
AKI	xxx xx.x%	xxx xx.x%	xxx xx.x%
Gastrointestinal bleeding	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hypertonic coma	xxx xx.x%	xxx xx.x%	xxx xx.x%
Pulmonary embolism	xxx xx.x%	xxx xx.x%	xxx xx.x%
Intracerebral hypertension/herniation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hydrocephalus	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hyperthermia	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other	xxx xx.x%	xxx xx.x%	xxx xx.x%
Day28 (± 3days)	xxx	xxx	xxx
Infection (respiratory)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (urinary)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (digest)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (other)	xxx xx.x%	xxx xx.x%	xxx xx.x%
AKI	xxx xx.x%	xxx xx.x%	xxx xx.x%
Gastrointestinal bleeding	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hypertonic coma	xxx xx.x%	xxx xx.x%	xxx xx.x%
Pulmonary embolism	xxx xx.x%	xxx xx.x%	xxx xx.x%
Intracerebral hypertension/herniation	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hydrocephalus	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hyperthermia	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other	xxx xx.x%	xxx xx.x%	xxx xx.x%
Any reported after hospital arrival*	xxx	xxx	xxx
Infection (respiratory)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (urinary)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (digest)	xxx xx.x%	xxx xx.x%	xxx xx.x%
Infection (other)	xxx xx.x%	xxx xx.x%	xxx xx.x%
AKI	xxx xx.x%	xxx xx.x%	xxx xx.x%
Gastrointestinal bleeding	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hypertonic coma	xxx xx.x%	xxx xx.x%	xxx xx.x%
Pulmonary embolism	xxx xx.x%	xxx xx.x%	xxx xx.x%
Intracerebral hypertension/herniation	xxx xx.x%	xxx xx.x%	xxx xx.x%

Hydrocephalus	xxx xx.x%	xxx xx.x%	xxx xx.x%
Hyperthermia	xxx xx.x%	xxx xx.x%	xxx xx.x%
Other	xxx xx.x%	xxx xx.x%	xxx xx.x%

Note:
** including baseline up to 28 day follow-up visit.*

Table 4. Study drug compliance

Study Medication [1]	Active drug (N =)	Placebo drug (N =)	Total (N =)
Duration of study treatment (days) [2]	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Duration of study treatment by category [2]	xxxx	xxxx	xxxx
1 – 7 days	xxx xx.x%	xxx xx.x%	xxx xx.x%
8 - 14 days	xxx xx.x%	xxx xx.x%	xxx xx.x%
15 - 21 days	xxx xx.x%	xxx xx.x%	xxx xx.x%
22 + days	xxx xx.x%	xxx xx.x%	xxx xx.x%
Bottles completed	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Complete >=80% of medication	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Complete all medication	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%

Note:
1 Only patients who completed study medication and have sufficient treatment information are included.
2 Duration >40 days is considered an error and not included

Table 5. Clinical assessment of outcomes over time

Variable Visits	Active drug (N =)	Placebo drug (N =)	Total (N =)
NIHSS			
Baseline	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Follow up 1 : 24h (± 3h)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Follow up 2 : Day 7 (± 1day)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Follow up 3 : Day 14 (± 2days)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Follow up 4 : Day 28 (± 3days)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
GCS			
Baseline	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Follow up 1 : 24h (± 3h)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx

Variable Visits	Active drug (N =)	Placebo drug (N =)	Total (N =)
Follow up 2 : Day 7 (± 1day)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Follow up 3 : Day 14 (± 2days)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Follow up 4 : Day 28 (± 3days)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
mRS			
Baseline	xxx	xxx	xxx
0: No symptoms	xxx xx.x%	xxx xx.x%	xxx xx.x%
1: No significant disability	xxx xx.x%	xxx xx.x%	xxx xx.x%
2: Slight disability	xxx xx.x%	xxx xx.x%	xxx xx.x%
3: Moderate disability	xxx xx.x%	xxx xx.x%	xxx xx.x%
4: Moderately severe disability	xxx xx.x%	xxx xx.x%	xxx xx.x%
5: Severe disability	xxx xx.x%	xxx xx.x%	xxx xx.x%
6: Dead	xxx xx.x%	xxx xx.x%	xxx xx.x%
Follow up 4 : Day 28 (± 3days)	xxx	xxx	xxx
0: No symptoms	xxx xx.x%	xxx xx.x%	xxx xx.x%
1: No significant disability	xxx xx.x%	xxx xx.x%	xxx xx.x%
2: Slight disability	xxx xx.x%	xxx xx.x%	xxx xx.x%
3: Moderate disability	xxx xx.x%	xxx xx.x%	xxx xx.x%
4: Moderately severe disability	xxx xx.x%	xxx xx.x%	xxx xx.x%
5: Severe disability	xxx xx.x%	xxx xx.x%	xxx xx.x%
6: Dead	xxx xx.x%	xxx xx.x%	xxx xx.x%
Follow up 5 : Day 90 (± 7days)	xxx	xxx	xxx
0: No symptoms	xxx xx.x%	xxx xx.x%	xxx xx.x%
1: No significant disability	xxx xx.x%	xxx xx.x%	xxx xx.x%

Variable Visits	Active drug (N =)	Placebo drug (N =)	Total (N =)
2: Slight disability	xxx xx.x%	xxx xx.x%	xxx xx.x%
3: Moderate disability	xxx xx.x%	xxx xx.x%	xxx xx.x%
4: Moderately severe disability	xxx xx.x%	xxx xx.x%	xxx xx.x%
5: Severe disability	xxx xx.x%	xxx xx.x%	xxx xx.x%
6: Dead	xxx xx.x%	xxx xx.x%	xxx xx.x%
Barthel Index (BI)			
Follow up 4 : Day 28 (± 3days)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Follow up 5 : Day 90 (± 7days)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
EQ-5D-5L VAS			
Follow up 4 : Day 28 (± 3days)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Follow up 5 : Day 90 (± 7days)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
EQ-5D-5L utility score (for survivors)			
Follow up 4 : Day 28 (± 3days)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Follow up 5 : Day 90 (± 7days)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx

Variable Visits	Active drug (N =)	Placebo drug (N =)	Total (N =)
EQ-5D-5L utility score (imputed death=0 score)			
Follow up 4 : Day 28 (± 3days)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Follow up 5 : Day 90 (± 7days)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Clinical Pulmonary Infection Score (CPIS)			
Baseline	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Day 3	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Day 7	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx

Table 6. Descriptive table of primary outcome and other secondary outcomes

Variable	Active drug (N =)	Placebo drug (N =)	Total (N =)
UW-mRS at day 90	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Secondary outcomes			
Death or disability at day 28 [1]	xxx xx.x%	xxx xx.x%	xxx xx.x%
Death or disability at day 90 [1]	xxx xx.x%	xxx xx.x%	xxx xx.x%
Death at day 28	xxx xx.x%	xxx xx.x%	xxx xx.x%
Death at day 90	xxx xx.x%	xxx xx.x%	xxx xx.x%
Disability at day 28 [1]	xxx xx.x%	xxx xx.x%	xxx xx.x%
Disability at day 90 [1]	xxx xx.x%	xxx xx.x%	xxx xx.x%
Any Stroke Associated Pneumonia (SAP)[2]	xxx xx.x%	xxx xx.x%	xxx xx.x%

Note:

1 *Death or disability, defined as mRS scores 4-6; Disability defined as mRS score 4-5.*

2 *SAP diagnosis standard: CPIS score>=6 from any visits of day 0, 3 and 7.*

Table 7. Image results (reported)

Variable	Intensive blood pressure lowering (N =)	Standard blood pressure lowering (N =)	Total (N =)
Initial imaging			
CT performed (Y/N)	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Time from onset to CT (hours)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Intracranial hematoma volume (ml)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Intraventricular hematoma (Y/N)	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Intraventricular hematoma volume (ml)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Edema (Y/N)	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Edema volume (ml)	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median (Q1; Q3)	xxx (xxx; xxx)	xxx (xxx; xxx)	xxx (xxx; xxx)
min max	xxx to xxx	xxx to xxx	xxx to xxx
Any hydrocephalus (Y/N)	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%
Any surgical history (Y/N)	xxx/xxx xx.x%	xxx/xxx xx.x%	xxx/xxx xx.x%

Table 8. Descriptive analysis of EQ-5D-5L at day 90

Visits EQ-5D-5L	Active drug (N =)	Placebo drug (N =)	Total (N =)
Day 90			
Mobility	N=xxx	N=xxx	N=xxx
1 : I have no problems in walking about	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2 : I have slight problems with walking around	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3 : I have moderate problems with walking around	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4 : I have severe problems with walking around	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5 : I am unable to walk around	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Self-care	N=xxx	N=xxx	N=xxx
1 : I have no problems with washing or dressing myself	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2 : I have slight problems with washing or dressing myself	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3 : I have moderate problems with washing or dressing myself	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4 : I have severe problems with washing or dressing myself	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5 : I am unable to wash or dress myself	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Usual activities	N=xxx	N=xxx	N=xxx
1 : I have no problems doing my usual activities	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2 : I have slight problems doing my usual activities	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3 : I have moderate problems doing my usual activities	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4 : I have severe problems doing my usual activities	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5 : I am unable to do my usual activities	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pain / discomfort	N=xxx	N=xxx	N=xxx
1 : I have no pain or discomfort	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2 : I have slight pain or discomfort	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3 : I have moderate pain or discomfort	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4 : I have severe pain or discomfort	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5 : I have extreme pain or discomfort	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Anxiety / depression	N=xxx	N=xxx	N=xxx
1 : I am not anxious or depressed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2 : I am slightly anxious or depressed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3 : I am moderately anxious or depressed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4 : I am severely anxious or depressed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5 : I am extremely anxious or depressed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

VAS (/100)	N=xxx	N=xxx	N=xxx
Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Median (Q1 – Q2)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Min - Max	xx – xx	xx – xx	xx – xx

Table 9. Clinical outcomes: model results

Outcome / analysis method	Primary model [1] N	Primary model [1] OR/MD (95% CI)	Primary model [1] P-value	Adjusted model [2] N	Adjusted model [2] OR/MD (95% CI)	Adjusted model [2] P-value
UW-mRS at Day 90 (continuous)						
Main, non-imputed model	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Sensitivity analyses						
Multiple imputations one (MAR) [3]	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Additional sensitivity analysis one [4]	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Additional sensitivity analysis two [4]	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Additional sensitivity analysis three [4]	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Secondary outcomes						
Utility-weighted mRS at day 180 (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Ordered mRS at day 28 (ordinal)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Ordered mRS at day 90 (ordinal)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Poor outcome [mRS 4-6] at Day 28 (binary)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Poor outcome [mRS 4-6] at Day 90 (binary)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Death at Day 28 [mRS 6] (binary)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Death at Day 90 [mRS 6] (binary)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Dependency at Day 28 [mRS 4-5] (binary)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Dependency at Day 90 [mRS 4-5] (binary)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
NIHSS at Day 1 (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
NIHSS at Day 7 (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Barthel index at Day 28 (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Barthel index at Day 90 (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
HRQoL measurements (survivors only)						

EQ-5D-5L visual analog scale at Day 28 (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
EQ-5D-5L utility score at Day 28 (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
EQ-5D-5L visual analog scale at Day 90 (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
EQ-5D-5L utility score at Day 90 (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
HRQoL measurements (impute death=0)						
EQ-5D-5L visual analog scale at Day 28 (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
EQ-5D-5L utility score at Day 28 (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
EQ-5D-5L visual analog scale at Day 90 (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
EQ-5D-5L utility score at Day 90 (continuous)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx
Any stroke-associated pneumonia (binary)	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx	xxxx	xx.xx (xx.xx to xx.xx)	0.xxx

(1) For ordinal, continuous and binary outcomes, the primary model consists in a generalised linear model with the appropriate distribution and link function. Unadjusted models include following fixed effects: randomised group, regions, hematoma location and NIHSS at admission.
(2) Adjusted models include the following additional baseline covariates: Age (continuous), mRS before stroke (categorical), sex (male vs female), time to randomisation (<12 vs ≥12 hours).
(3) Referring to section 5.4.4
(4) Referring to section 5.4.6

Programming notes:
- *add/edit footnotes as appropriate*
- *for the analysis of dependency alone, restrict denominator to subjects who are alive (mRS 0-5) at corresponding timepoints.*

Table 10. Multiplicity adjustment

Secondary outcomes	P-value from the model	number of comparisons remain	adjusted significance level (Holm-Sidak)	Conclusion *
Ordered mRS at day 90 (ordinal)	xxx	8	0.0064	xxx
Poor outcome [mRS 4-6] at Day 90 (binary)	xxx	7	0.0073	xxx
Death at Day 90 [mRS 6] (binary)	xxx	6	0.0085	xxx
Dependency at Day 90 [mRS 4-5] (binary)	xxx	5	0.0102	xxx
NIHSS at Day 7 (continuous)	xxx	4	0.0127	xxx
Barthel index at Day 90 (continuous)	xxx	3	0.0170	xxx
EQ-5D-5L utility score at Day 90 (continuous)	xxx	2	0.0253	xxx
Any stroke-associated pneumonia (binary)	xxx	1	0.05	xxx

Note:
** Conclusion includes Remain significant, Change to non-significant, Remain non-significant*

Table 11. Adverse events

Event	Active drug (N =)	Placebo drug (N =)	P-value
Number of adverse events (AE)	**nEVT nPT(xx.x%)**	**nEVT nPT(xx.x%)**	**0.xx**
Relation to Treatment			
Definitely related	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Possibly related	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Probably not relevant	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Definitely irrelevant	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Unable to determine	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Number of serious adverse events (SAE)	**nEVT nPT(xx.x%)**	**nEVT nPT(xx.x%)**	**0.xx**
Relation to Treatment			
Definitely related	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Possibly related	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Probably not relevant	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Definitely irrelevant	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Unable to determine	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Number of AE of special interest (AESI)	**nEVT nPT(xx.x%)**	**nEVT nPT(xx.x%)**	**0.xx**
Type of AESI			
Hematoma enlargement (>6mL or 33%)	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	**0.xx**
New intracranial hematoma	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	**0.xx**
Diarrhea	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	**0.xx**
Abnormal laboratory test result	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	**0.xx**
Relation to Treatment			
Definitely related	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Possibly related	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Probably not relevant	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Definitely irrelevant	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Unable to determine	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	

Programming note:
SAEs will be summarised as the number (nPT) and proportion of patients experiencing at least one event. In addition, the total number of events (nEVT) will be reported. P-value from logistic regression.
Conducted in ITT population and repeat in PP population.

Table 12. Causes of death (if available)

Cause	Active drug (N =)	Placebo drug (N =)
All patients		
Primary cause of death	N=XXX	N=XXX
Most common cause #1	nnn xx%	nnn xx%
Most common cause #2	nnn xx%	nnn xx%
Etc.		
Most common cause #10	nnn xx%	nnn xx%
All other causes	nnn xx%	nnn xx%
Underlying causes of death	N=XXX	N=XXX
Most common cause #1	nnn xx%	nnn xx%
Most common cause #2	nnn xx%	nnn xx%
Etc.		
Most common cause #10	nnn xx%	nnn xx%
All other causes	nnn xx%	nnn xx%

Programming notes:

- *Order causes of death by descending frequency.*
- *Do not list categories with 0 deaths.*
- *Use number who died*
- *Depending on the distribution of deaths, we may choose to only report the x (e.g. 10) most common in the publication; however, the original table should include all causes with at least one patient.*
- *Conducted in ITT population*

Table 13. Protocol violations and deviations (if available)

Cause	Active drug (N =)	Placebo drug (N =)
Eligibility violations	N=XXX	N=XXX
Age <18 years	nnn xx%	nnn xx%
Final diagnosis was not spontaneous ICH	nnn xx%	nnn xx%
Randomised >48 hours after stroke onset	nnn xx%	nnn xx%
NIHSS <8 and GCS 15	nnn xx%	nnn xx%
Etc.	nnn xx%	nnn xx%
Non-compliance with intervention	N=XXX	N=XXX
Patients who were found later in the trial to have received incorrect treatment or incorrect dose of the allocated study drug after confirmation by local investigators.	nnn xx%	nnn xx%
Other major protocol violations which have been adjudicated, for example concomitant TCM contains same components of FYTF-919.	nnn xx%	nnn xx%
Etc.	nnn xx%	nnn xx%
Primary outcome	N=XXX	N=XXX
Missing outcome assessment	nnn xx%	nnn xx%
Lost to follow-up	nnn xx%	nnn xx%
Etc.	nnn xx%	nnn xx%

Programming notes:

- *Reasons for non-compliance and missing outcome will be defined while blinded.*

a. Figures

Figure 1: Consort flowchart

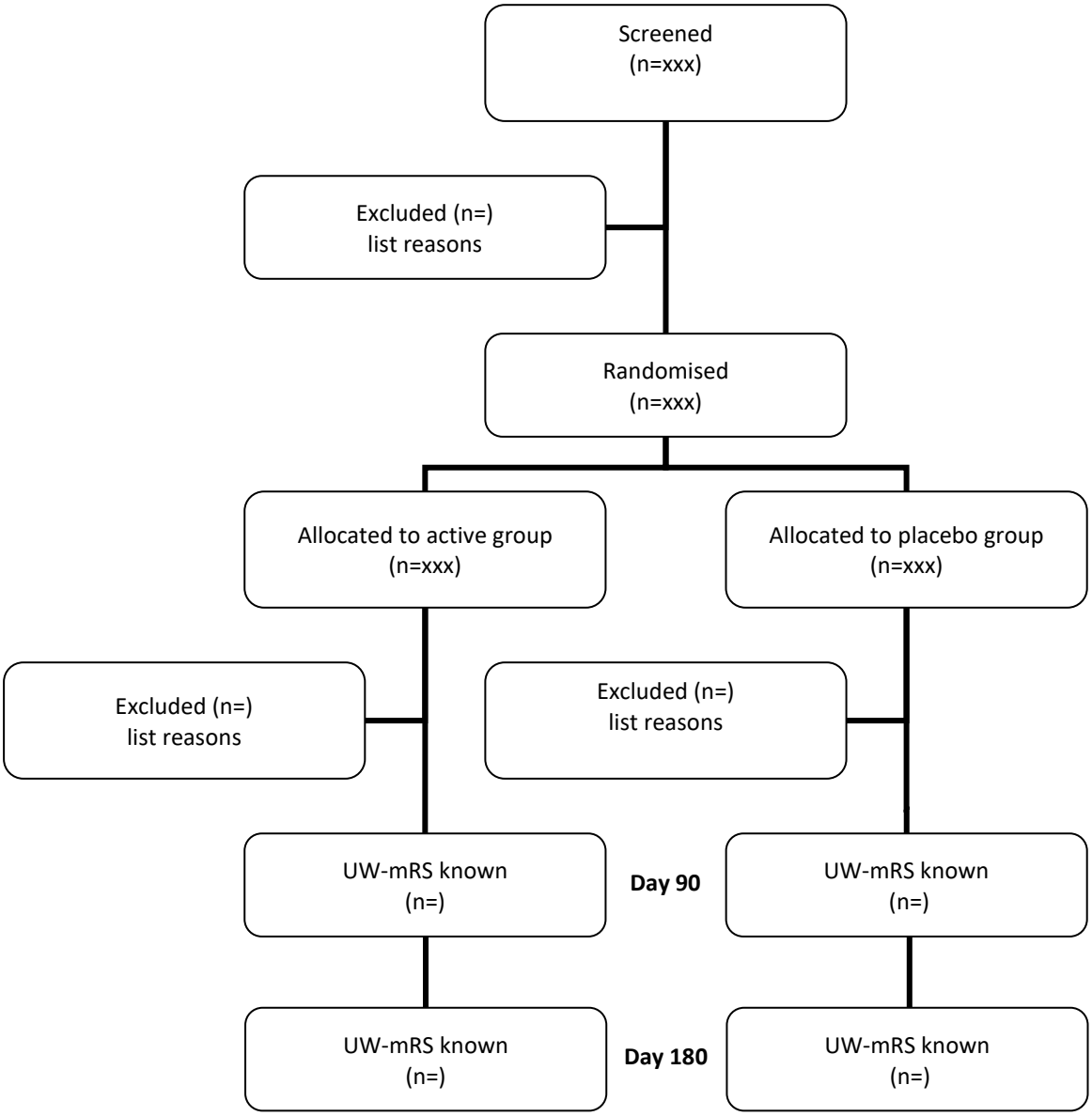

Figure 2. Grotta bar charts of mRS

Programming note: Stacked bar chart with 2 bars (active vs placebo) per visit. Each bar to be of the same high (100%). Show the proportion in each category using labels on the bars.

Figure 3. Boxplot of NIHSS by follow-up assessment

Figure 4. Forest plot for subgroup analysis of UW-mRS at 90 days

Programming note: add number of subjects, estimated mean difference, SE, and P value for interaction.

b. Listings

Listing 1. Protocol deviations (if available)

Site ID	Patient ID	Date	Type of deviation	Description	Corrective action taken

Listing 2. Serious adverse events

Site ID	Patient ID	Date	Event description	Event code	Relationship with treatment	Outcome