順天醫藥生技股份有限公司

(TPEX:6535)

2025/10

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LT3001

治療急性缺血性中風的創新小分子藥物

開發進度

預計2025年啟動中國CDE與美國FDA的臨床三期法規諮詢

並於2026年啟動中國臨床三期試驗收案

預計2030中國上市

LT3001 開發目標 – 效果更好、更安全 - 使用群更廣的中風新藥

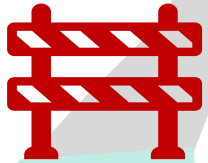
未被滿足醫療需求

急性缺血性中風的藥物治療困境 (IV tPA unmet need):

1. **腦出血副作用 (2~6%)**
2. **能使用的病人少 (<10%)**

tPA全球銷售 每年20億美金

4.5小時



LT3001的開發目標:

更安全、效果更好、嘉惠更多AIS病人

>5x時間窗、不用滿足特殊影像條件

銷售峰值60-80億美金

ACTIVASE rt-PA
– IV tPA 靜脈溶栓劑 **使用說明書**

1 INDICATIONS

ACTIVASE rt-PA (alteplase for injection) is indicated for: ①

- The management of **acute ischemic stroke** (AIS) in adults for improving neurological recovery and reducing the incidence of disability. Treatment should only be initiated within 3 hours after the onset of stroke symptoms, and after exclusion of intracranial hemorrhage by a cranial computerized tomography (CT) scan or other diagnostic imaging method sensitive for the presence of hemorrhage. Eligibility criteria of the National Institute of Neurological Disorders and Stroke (NINDS) protocol must be strictly adhered to (see 2 CONTRAINDICATIONS).

美國心臟學會 - 急性缺血性中風治療指南 (2019):

Table 8. Eligibility Recommendations for IV Alteplase in Patients With AIS

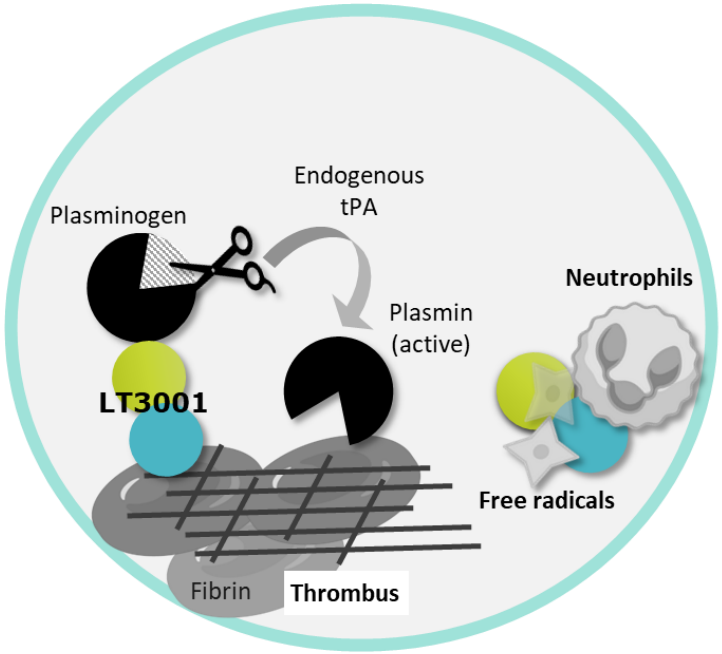
Indications (COR I)		
Within 3 h*	①	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is recommended for selected patients who may be treated within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in this table to determine patient eligibility.† (*COR I; LOE A*)
3–4.5 h*	②	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is also recommended for selected patients who can be treated within 3 and 4.5 h of ischemic stroke symptom onset or patient last known well. Physicians should review the criteria outlined in this table to determine patient eligibility.† (*COR I; LOE B-R*)§
Additional recommendations for treatment with IV alteplase for patients with AIS (COR IIa)		And (COR IIb)
Wake-up and unknown time of onset	③	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) administered within 4.5 h of stroke symptom recognition can be beneficial in patients with AIS who awake with stroke symptoms or have unclear time of onset >4.5 h from last known well or at baseline state and who have a DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR. (*COR IIa; LOE B-R*)‡

治療時間窗	接受治療需滿足的影像學條件	效果: 完全恢復 mRS=0-1		效果: 可生活自理、工作 mRS=0-2		安全: 症狀性腦出血 sICH
① **0-3 小時** (NINDS, US, 1995)	一般斷層掃描 (排除出血型中風)	tPA (n=168): 39% vs placebo (n=165): 26% (p=0.019)	**+13%**	NA		**tPA: 6.4%** placebo: 0.6% (p<0.001)
② **3-4.5 小時** (ECASS 3, EU, 2008)		tPA (n=418): 52% vs placebo (n=403): 45% (p=0.04)	**+7%**	tPA: 66.5% vs placebo 61.5%	**+5%**	**tPA: 2.4%** placebo: 0.2% (p=0.008)
③ **Wake-up Stroke** (WAKE-UP, EU, 2018)	核磁 MRI mismatch	tPA (n=254): 53% vs placebo (n=249): 42% (p=0.02)	**+11%**	tPA: 74% vs placebo 65%	**+9%**	**tPA: 2.4%** placebo: 0.4% (p=0.1)
4.5-9 小時 (Extend, Australian, 2019)	斷層顯影 CTP mismatch	tPA (n=113): 35.4% vs placebo (n=112): 29.5% (p=0.04)	**+6%**	tPA:49.6% vs placebo:42.6%,	**+7%**	**tPA: 6.2%** placebo: 0.9% (p=0.053)
4.5-24 小時 LT3001	一般斷層掃描 (排除出血型中風)	**+ > 6%**		**+ > 7%**		**0%**

LT3001機會 - 溶栓但不出血+腦保護 - 可連續給予多天, 持續改善腦細胞功能

創新的溶栓機制 (MoA):

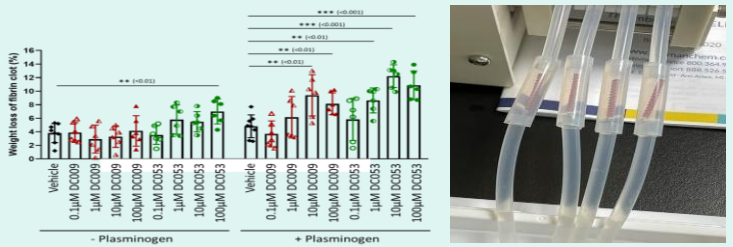
LT3001 可直接結合於纖維蛋白血栓與纖溶酶原，將纖溶酶原富集於血栓處，靶向增強內源性纖溶作用。



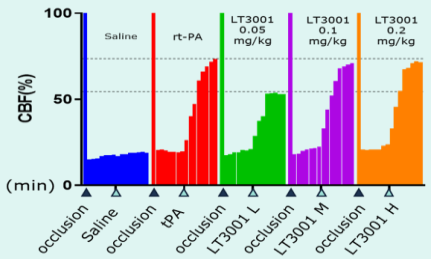
- **中國首都醫科大學彭師奇/趙明教授**發明,
- 臨床前研究由**美國哈佛大學醫學院**神經保護研究室**Prof. Eng Lo**實驗室完成並發表.

(JMCB. 2016, Translational Stroke Res. 2022)

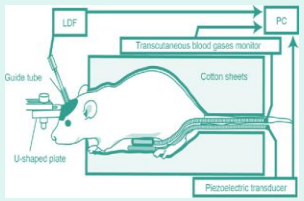
體外實驗 — 顯示血栓體積隨加入LT3001劑量增加明顯縮小



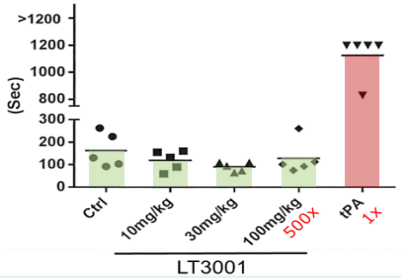
動物實驗 — LT3001有效恢復血栓閉塞動脈中的腦灌注



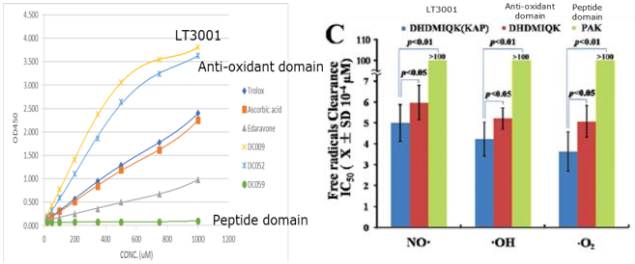
Cerebral blood flow



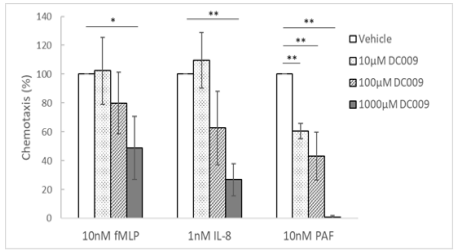
動物實驗 — 不延長出血時間



具有強效抗氧化及清除自由基活性

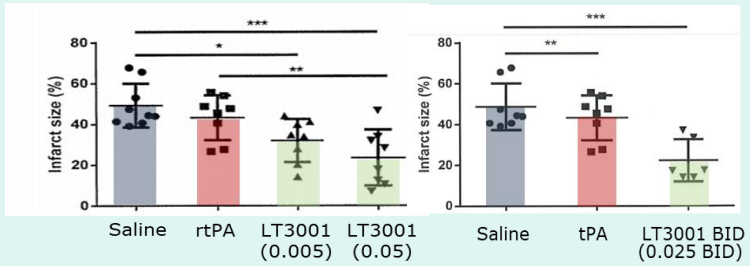


可減少中性粒細胞浸潤

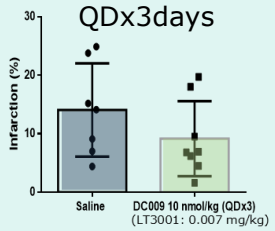


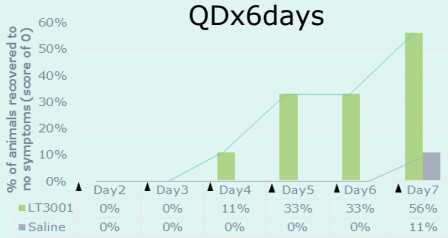
呈現出劑量依賴性地縮小梗死體積，並改善神經功能結局；
相較於 tPA，療效更優，尤其在超出標準治療時間窗後啟動治療時，效果更為顯著。

Treated at **3 hour** after stroke onset



Treated at **24 hour** after stroke onset

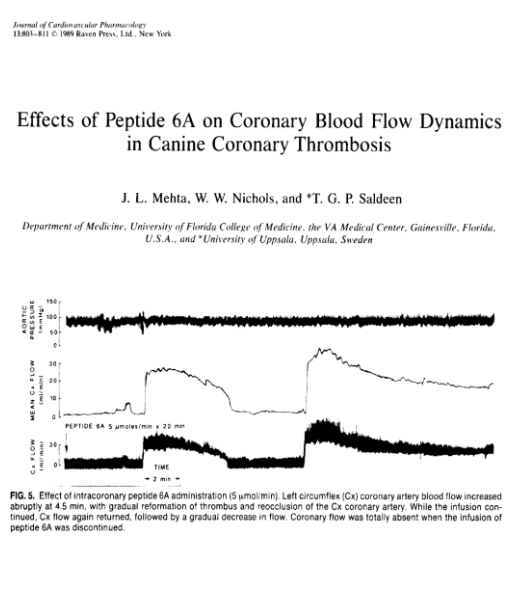




LT3001重點文獻 - 全球合作 - 分子設計至臨床2a結果

LT3001溯源

本品所基於的**內源性溶栓肽**由瑞典Saldeen教授團隊于**1980**年代首次發現, 並在犬冠狀動脈阻塞模型中驗證其溶栓療效.



Journal of Cardiovascular Pharmacology
13:803–811 © 1989 Raven Press, Ltd., New York

Effects of Peptide 6A on Coronary Blood Flow Dynamics in Canine Coronary Thrombosis

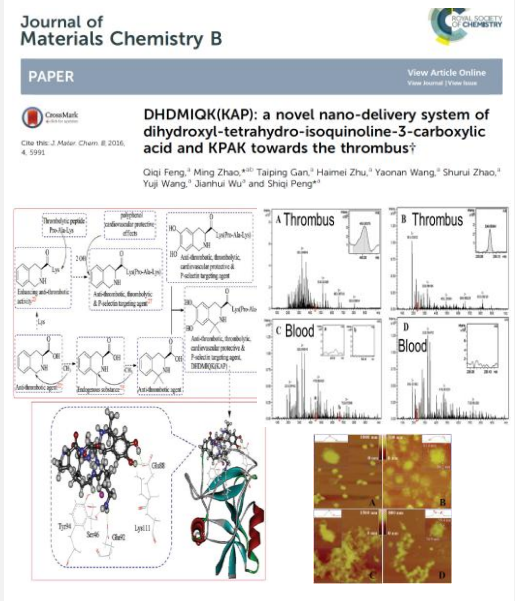
J. L. Mehta, W. W. Nichols, and *T. G. P. Saldeen

*Department of Medicine, University of Florida College of Medicine, the VA Medical Center, Gainesville, Florida, U.S.A., and *University of Uppsala, Uppsala, Sweden*

FIG. 5. Effect of intracoronary peptide 6A administration (5 μmol/min). Left circumflex (Cx) coronary artery blood flow increased abruptly at 4.5 min, with gradual reformation of thrombus and reocclusion of the Cx coronary artery. While the infusion continued, Cx flow again returned, followed by a gradual decrease in flow. Coronary flow was totally absent when the infusion of peptide 6A was discontinued.

功能優化與結構創新

由首都醫科大學彭師奇教授與趙明教授團隊開發, **賦予其自由基清除、抗炎及血栓靶向功能**, 正式確立為候選藥物LT3001. 成果發表於**2016**年



Journal of Materials Chemistry B

PAPER

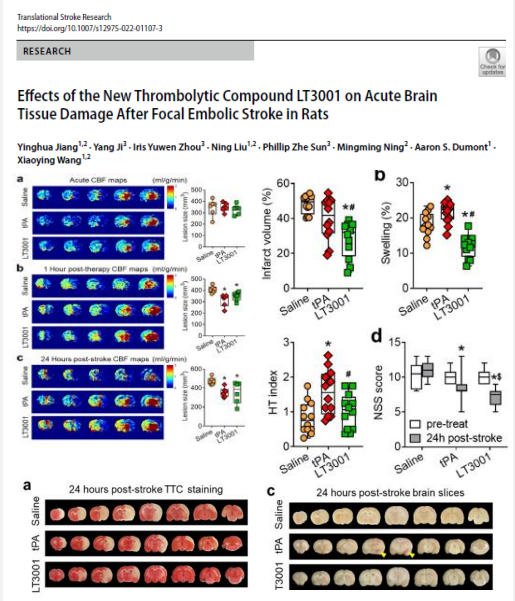
View Article Online

DHDMIQK(KAP): a novel nano-delivery system of dihydroxyl-tetrahydro-isoquinoline-3-carboxylic acid and KPAK towards the thrombus†

Qiqi Feng,[a] Ming Zhao,*[a,b] Taiping Gan,[a] Haimei Zhu,[a] Yaonan Wang,[a] Shurui Zhao,[a] Yuji Wang,[a] Jianhui Wu[a] and Shiqi Peng*[a]

臨床前驗證

哈佛大學醫學院 Eng Lo教授團隊開展的臨床前研究顯示, **LT3001療效優於tPA, 且超窗後仍安全具活性.** 成果發表於**2022**年.



Translational Stroke Research
https://doi.org/10.1007/s12975-022-01107-3

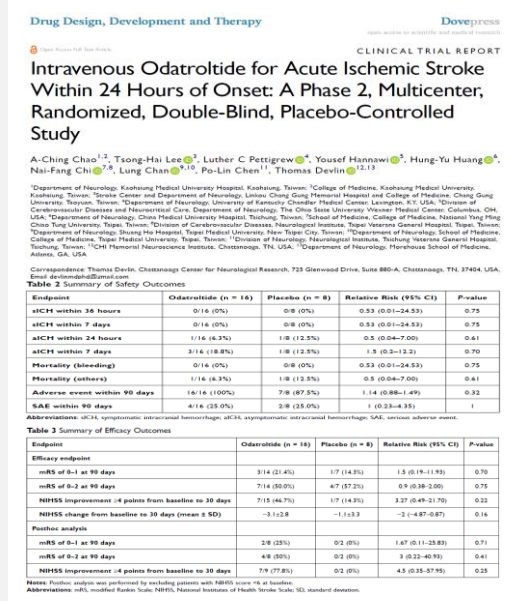
RESEARCH

Effects of the New Thrombolytic Compound LT3001 on Acute Brain Tissue Damage After Focal Embolic Stroke in Rats

Yinghua Jiang[1,2] · Yang Ji[3] · Iris Yuwen Zhou[2] · Ning Liu[1,2] · Phillip Zhe Sun[2] · Mingming Ning[2] · Aaron S. Dumont[1] · Xiaoying Wang[1,2]

早期臨床試驗成果

LT3001-201(二A期, n=24)研究顯示, 於**LKN<24小時AIS病患單次給藥耐受性良好**, 並呈現神經功能改善趨勢, 成果已於**2024**年發表.



Drug Design, Development and Therapy

Dovepress

CLINICAL TRIAL REPORT

Intravenous Odatroltide for Acute Ischemic Stroke Within 24 Hours of Onset: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study

A-Ching Chao[1,2], Tsong-Hai Lee[3], Luther C Pettigrew[4], Yousef Hannawi[5], Hung-Yu Huang[6], Nai-Fang Chi[7,8], Lung Chan[9,10], Po-Lin Chen[11], Thomas Devlin[12,13]

Table 2 Summary of Safety Outcomes

Endpoint	Odatroltide (n = 16)	Placebo (n = 8)	Relative Risk (95% CI)	P-value
sICH within 36 hours	0/16 (0%)	0/8 (0%)	0.53 (0.01–24.53)	0.75
sICH within 7 days	0/16 (0%)	0/8 (0%)	0.53 (0.01–24.53)	0.75
sICH within 24 hours	1/16 (6.3%)	1/8 (12.5%)	0.5 (0.04–7.00)	0.61
sICH within 7 days	3/16 (18.8%)	1/8 (12.5%)	1.5 (0.2–12.2)	0.70
Mortality (bleeding)	0/16 (0%)	0/8 (0%)	0.53 (0.01–24.53)	0.75
Mortality (others)	1/16 (6.3%)	1/8 (12.5%)	0.5 (0.04–7.00)	0.61
Adverse event within 90 days	16/16 (100%)	7/8 (87.5%)	1.14 (0.88–1.49)	0.32
SAE within 90 days	4/16 (25.0%)	2/8 (25.0%)	1 (0.23–4.35)	1

Abbreviations: sICH, symptomatic intracranial hemorrhage; aICH, asymptomatic intracranial hemorrhage; SAE, serious adverse event.

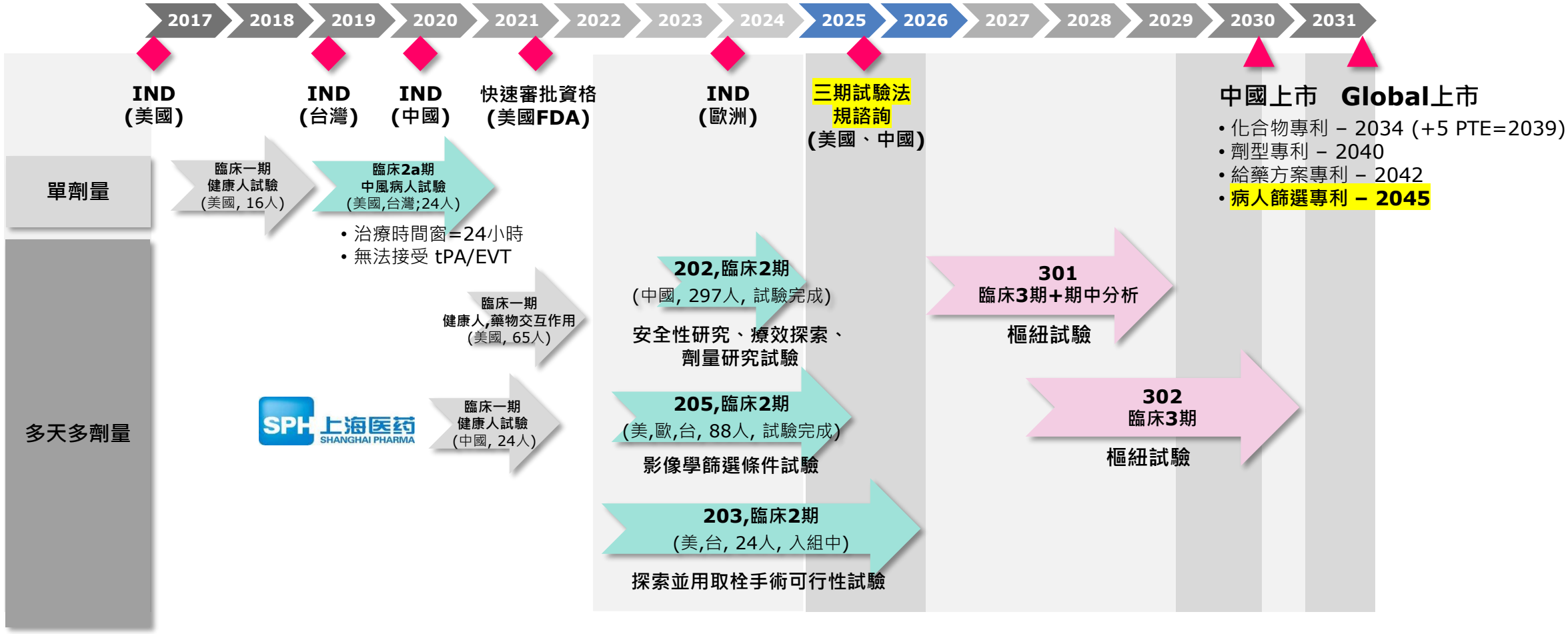
Table 3 Summary of Efficacy Outcomes

Endpoint	Odatroltide (n = 16)	Placebo (n = 8)	Relative Risk (95% CI)	P-value
Efficacy endpoint				
mRS of 0–1 at 90 days	3/14 (21.4%)	1/7 (14.3%)	1.5 (0.19–11.93)	0.70
mRS of 0–2 at 90 days	7/14 (50.0%)	4/7 (57.2%)	0.9 (0.38–2.00)	0.75
NIHSS improvement ≥4 points from baseline to 30 days	7/15 (46.7%)	1/7 (14.3%)	3.27 (0.49–21.70)	0.22
NIHSS change from baseline to 30 days (mean ± SD)	−9.1±2.8	−1.1±3.3	−2 (−4.87–0.87)	0.16
Posthoc analysis				
mRS of 0–1 at 90 days	2/8 (25%)	0/2 (0%)	1.67 (0.11–25.83)	0.71
mRS of 0–2 at 90 days	4/8 (50%)	0/2 (0%)	3 (0.22–40.93)	0.41
NIHSS improvement ≥4 points from baseline to 30 days	7/9 (77.8%)	0/2 (0%)	4.5 (0.35–57.95)	0.25

Notes: Posthoc analysis was performed by excluding patients with NIHSS score =6 at baseline.
Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

LT3001 臨床開發計畫 – 完成多個全球一、二期試驗 – 證明產品安全性、有效性

- 治療時間窗=中風發生後24小時



A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Multiple Doses of LT3001 in Patients with Acute Ischemic Stroke (AIS)

Leading Site : Beijing Tiantan Hospital, Capital Medical University

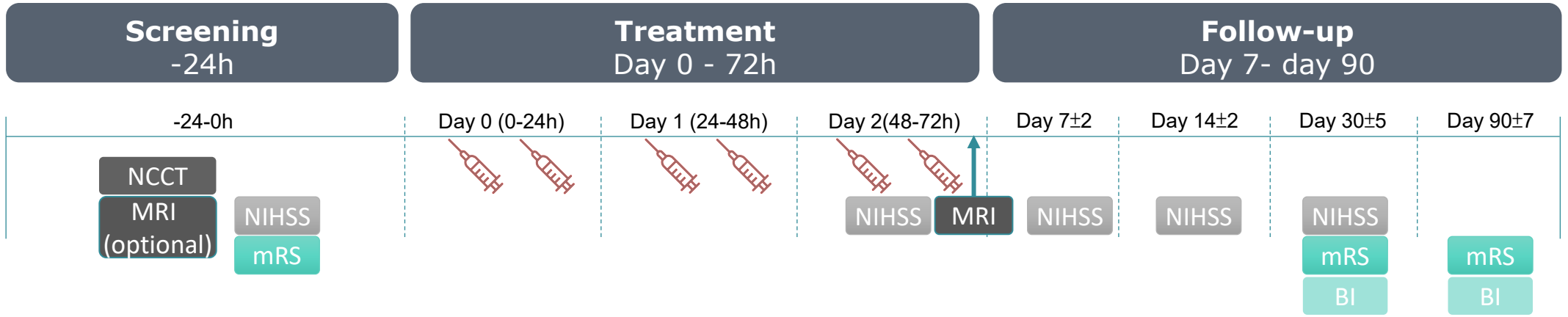
Leading PI : Professor Yongjun Wang

Sponsor : Shanghai Pharmaceuticals Holding Co., Ltd.

Study Period : 2023/4/6 ~ 2024/9/27

LT3001-202: Study Design

A multicenter, randomized, double-blind, placebo-controlled phase 2 clinical trial in China



Primary I/E Criteria:

- AIS
- Age 18-80
- Baseline NIHSS=4-25
- LKN<24h
- Exclude patients receiving or planned for EVT or IV thrombolytics.

R

N=300
1:1:1

- LT3001 Full-dose 0.05 mg/kg
- LT3001 Half-dose 0.025 mg/kg
- Placebo

30min-IV infusion

- **Primary Endpoint – Safety**
  - Incidence of AEs and ADRs within 90 days post-first dose.
  - Number and incidence of symptomatic or asymptomatic intracranial hemorrhages within 3 days post-first dose.
- **Secondary Endpoint – Efficacy**
  - mRS, NIHSS, BI

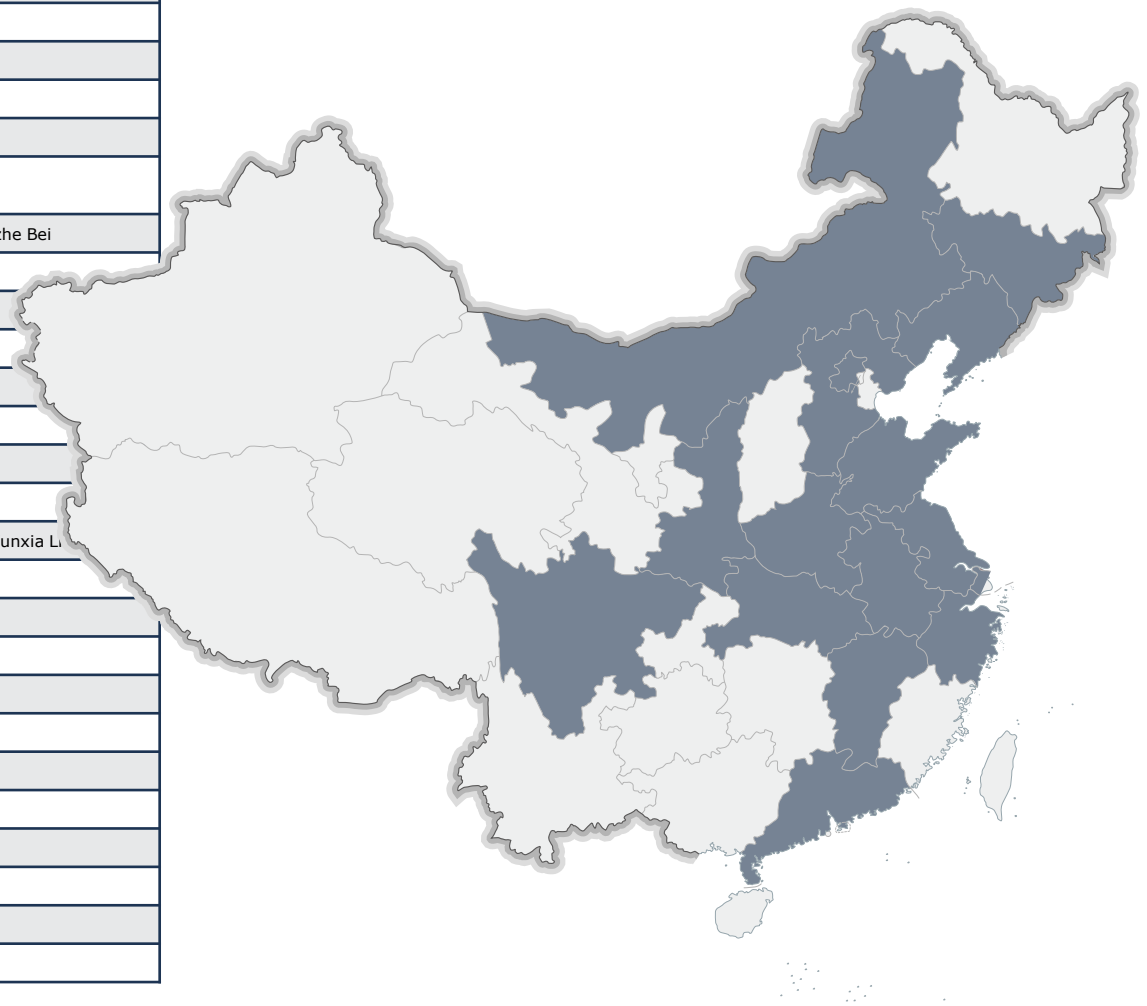
- The sample size of this study had been determined by referring to the sample size of Phase 2 of other drugs for AIS treatment, combined with the new drug clinical development experience of clinical research experts
- Central randomized with stratification factor of ① baseline MRI (Y/N), ②baseline NIHSS of 4~6, 7~10, 11~25

From April 2023 to July 2024, 301 subjects were enrolled across 28 medical centers; 297 were randomized and received study drug.

List of Study Sites and Investigators

Site Name	Investigator
Beijing Tiantan Hospital, Capital Medical University (Leading site)	Yongjun Wang
The First Hospital of Jilin University	Yi Yang
The First Affiliated Hospital of Jinan University (Guangzhou Overseas Chinese Hospital)	Anding Xu
Beijing Tsinghua Changgung Hospital	Jian Wu
Beijing Luhe Hospital, Capital Medical University	Yanling Wang
Daqing Oilfield General Hospital	Jianghua Liu
Beipiao Central Hospital	Yutong Ma
The First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology	Bo Liu
Baogang Hospital of Inner Mongolia	Dong Wang/Hongzhe Bei
People's Hospital of Hengshui (Harrison International Peace Hospital)	Yan Wei
Luoyang Third People's Hospital	Bing Sun
Xi'an Gaoxin Hospital	Yi Jia
Liaocheng People's Hospital	Cunju Guo/Lin Ma
Huai'an Second People's Hospital	Liandong Zhao
The Affiliated Hospital of Xuzhou Medical University	Deqin Geng
The Second Affiliated Hospital of Soochow University	Chunfeng Liu
Shanghai Pudong Hospital	Shuangxing Hou/Yunxia Li
Zhongnan Hospital of Wuhan University	Yumin Liu
Zhejiang Hospital	Yaguo Li
Taizhou First People's Hospital	Zhimin Wang
Taizhou Municipal Hospital	Hao Xu
Pingxiang People's Hospital	Fei Yi
Xianyang Hospital of Yan'an University	Lei Lei
Linfen Central Hospital	Hongguo Dai
Linfen People's Hospital	Junfang Hao
Central People's Hospital of Zhanjiang	Hui Mai
Nanshi Hospital of Nanyang	Bin Liu
The Third Hospital of Mianyang	Diwen Zhang

A total of 28 study sites participated in this study and had subjects enrolled.



LT3001-202: Baseline Demographic

- LT3001-202 enrolled 297 AIS patients (median age 63, ~70% male) with median baseline NIHSS 8. The majority were treated >12 h from onset (Q1–Q3 ~11–20 h, up to 24 h). ~55% were moderate strokes and ~55–60% LAA etiology, balanced across groups.

		0.05 mg/kg	0.025 mg/kg	Placebo
N		99	96	102
區域分佈	Yrs, median (Q1, Q3) Yrs, mean (SD)	65 (59,73) 63.6 (10.6)	64 (56,70) 62.5 (10.0)	63 (56,72) 62.8 (10.2)
年齡	Male%	70.7%	68.8%	71.6%
性別	Kg, median (Q1, Q3) Kg, mean (SD)	68 (60,75) 68.47 (10.30)	70 (60,79) 68.87 (11.64)	70 (60,75) 68.51 (11.63)
體重	h, median (Q1, Q3) h, mean (SD)	12.44 (11.07, 16.42) 13.83 (4.29)	11.81 (10.59, 19.80) 14.41 (5.39)	12.15 (10.77, 20.02) 14.74 (5.31)
發病至首次用藥時間	median (Q1, Q3) (Min, Max) mean (SD)	8 (6, 10) (4, 15) 8.4 (2.5)	8 (7, 10) (4, 16) 8.5 (2.5)	8 (6, 10) (4, 17) 8.4 (2.8)
基線**NIHSS**評分	N (%)	25 (25.3%)	20 (20.8%)	27 (26.5%)
4～6分	N (%)	56 (56.6%)	55 (57.3%)	55 (53.9%)
7～10分	N (%)	18 (18.2%)	21 (21.9%)	20 (19.6%)
11～25分				
中風分型	N (%)	52 (53.1%)	56 (58.3%)	61 (59.8%)
大動脈粥樣硬化型 **(LAA)**	N (%)	1 (1%)	2 (2.1%)	2 (2%)
心源性栓塞型 **(Embolic)**	N (%)	44 (44.9%)	38 (39.6%)	38 (37.3%)
小動脈閉塞型 **(SAO)**	N (%)	0	0	0
其他明確病因型 **(Others)**	N (%)	1 (1%)	0	1 (1%)

LT3001-202 Safety Result: No Increased Risk of sICH

- **Primary Endpoint** :
  - LT3001 was well tolerated across all dose groups.
  - The incidence of adverse events (AEs) and adverse drug reactions (ADRs) within 90 days after first dosing was similar among the high-dose LT3001, low-dose LT3001, and placebo groups, with most events being mild.
  - No symptomatic intracranial hemorrhage occurred in any group within 3 days after first dosing.
  - Three cases of asymptomatic intracranial hemorrhage were reported — all in the placebo group.

Proportion of Subjects with Asymptomatic Intracranial Hemorrhage (ICH) Within 3 Days After First Dose

		0.05 mg/kg	0.025 mg/kg	Placebo
N		99	96	102
Asymptomatic ICH	N (%)	0	0	3 (2.9%)
HI Type 1	N (%)	0	0	1 (1%)
HI Type 2	N (%)	0	0	2 (2%)
PH Type 1	N (%)	0	0	0
PH Type 2	N (%)	0	0	0

LT3001-202 Efficacy: mRS=0-1, mRS=0-2, NIHSS outcome

1. Favorable indicators were observed in mRS0-1, mRS0-2, and NIHSS results.
2. An 7.3% enhancement in mRS0-2 was detected in all study population.
3. Early improvement in NIHSS scores, signaling reperfusion, has been consistently observed.

		LT3001 0.05 mg/kg	LT3001 0.025 mg/kg	Placebo	0.05 - Placebo	0.025 - Placebo
All	n	99	96	102		
	mRS 0-1, d90	67.7%	69.8%	66.7%	**1.1%**	**5.3%**
	mRS 0-2, d90	85.9%	80.2%	78.4%	**7.3%**[1]	**3.4%**
	NIHSS Improvement*	71.7%	71.9%	65.7%	**5.3%**	**5.6%**

[1]RR = 1.1 (95% CI: 1.0, 1.2) marginal statistical difference.
*NIHSS reduced ≥4 points and/or achieved ≤1 on d14 in patients had completed d14 assessment.

LT3001-202 Efficacy: Stroke Severity Subgroups

1. Moderate strokes (NIHSS 7–10) were well represented (≥50 participants per group) and showed consistent efficacy, with a +9% improvement in 90-day mRS across both dose levels.
2. The 0.05 mg/kg dose demonstrated greater therapeutic potential than 0.025 mg/kg in patients with moderate-to-severe strokes (NIHSS 11–25).

		LT3001 0.05 mg/kg	LT3001 0.025 mg/kg	Placebo	0.05 - Placebo	0.025 - Placebo
Mild Stroke Baseline NIHSS 4~6	n	25	20	27		
	mRS 0-1, d90	88.0%	90.0%	88.9%	**-0.9%**	**1.1%**
	mRS 0-2, d90	96.0%	90.0%	96.3%	**-0.3%**	**-6.3%**
Moderate Stroke Baseline NIHSS 7~10	n	56	55	55		
	mRS 0-1, d90	69.6%	76.4%	67.3%	**2.4%**	**9.1%**
	mRS 0-2, d90	87.5%	87.3%	78.2%	**9.3%[1]**	**9.1%[2]**
Moderate-severe Stroke Baseline NIHSS 11~25	n	18	21	20		
	mRS 0-1, d90	38.9%	38.1%	35.0%	**3.9%**	**3.1%**
	mRS 0-2, d90	66.7%	42.9%	55.0%	**11.7%**	**-12.1%**

[1]RR = 1.1 (95% CI: 1.0, 1.4) [2]RR = 1.2 (95% CI: 1.0, 1.4)

LT3001-202 Efficacy: TOAST Subgroups

- LT3001 shows potential for a better treatment effect in AIS patients with large artery atherosclerosis (LAA) compared to small artery occlusion (SAO) based on their TOAST classification upon hospital presentation.

		LT3001 0.05 mg/kg	LT3001 0.025 mg/kg	Placebo	0.05 mg/kg - Placebo	0.025 mg/kg - Placebo	Combined - Placebo
Large artery atherosclerosis (LAA)	n	52	56	61			
	mRS 0-1, d90	61.5%	66.1%	57.4%	**4.1%**	**8.7%**	**+6.5%**
	mRS 0-2, d90	75.0%	76.8%	65.6%	**9.4%**	**11.2%**	**+10.4%**
Small artery occlusion (SAO)	N	44	38	38			
	mRS 0-1, d90	70.5%	71.1%	76.3%	-5.9%	-5.3%	-5.6%
	mRS 0-2, d90	86.4%	78.9%	92.1%	-5.7%	-13.2%	-9.2%

*post-hoc analysis was performed by non-imputation dataset.

LT3001-202 Efficacy: Disabling Stroke Subgroups

- LT3001 shows potential for a better treatment effect in AIS patients with disabling stroke, such as arm motor drift, and leg motor drift, based on their baseline NIHSS deficits upon hospital presentation.

		LT3001 0.05 mg/kg	LT3001 0.025 mg/kg	Placebo	0.05 mg/kg - Placebo	0.025 mg/kg - Placebo	Combined - Placebo
Arm motor drift Baseline NIHSS #5>2	n	30	30	31			
	mRS 0-1, d90	36.7%	53.3%	29%	**7.7%**	**24.3%**	**+16.0%**
	mRS 0-2, d90	63.3%	63.3%	41.9%	**21.4%**	**21.4%**	**+21.4%**
Leg motor drift Baseline NIHSS #6>2	n	38	35	37			
	mRS 0-1, d90	47.4%	57.1%	43.2%	**4.2%**	**13.9%**	**+8.8%**
	mRS 0-2, d90	71.1%	68.6%	56.8%	**14.3%**	**11.8%**	**+13.1%**
Arm or leg motor drift Baseline NIHSS #5>2 or #6>2	n	43	36	40			
	mRS 0-1, d90	46.5%	55.6%	42.5%	**4.0%**	**13.1%**	**+8.1%**
	mRS 0-2, d90	69.8%	66.7%	55%	**14.9%**	**11.7%**	**+13.4%**
Aphasia Baseline NIHSS #9≥1	n	51	41	45			
	mRS 0-1, d90	62.7%	68.3%	55.6%	**7.1%**	**12.7%**	**+9.7%**
	mRS 0-2, d90	78.4%	75.6%	62.2%	**16.2%**	**13.4%**	**+15.0%**

*post-hoc analysis was performed by non-imputation dataset.

Key Takeaways from the LT3001-202 Study

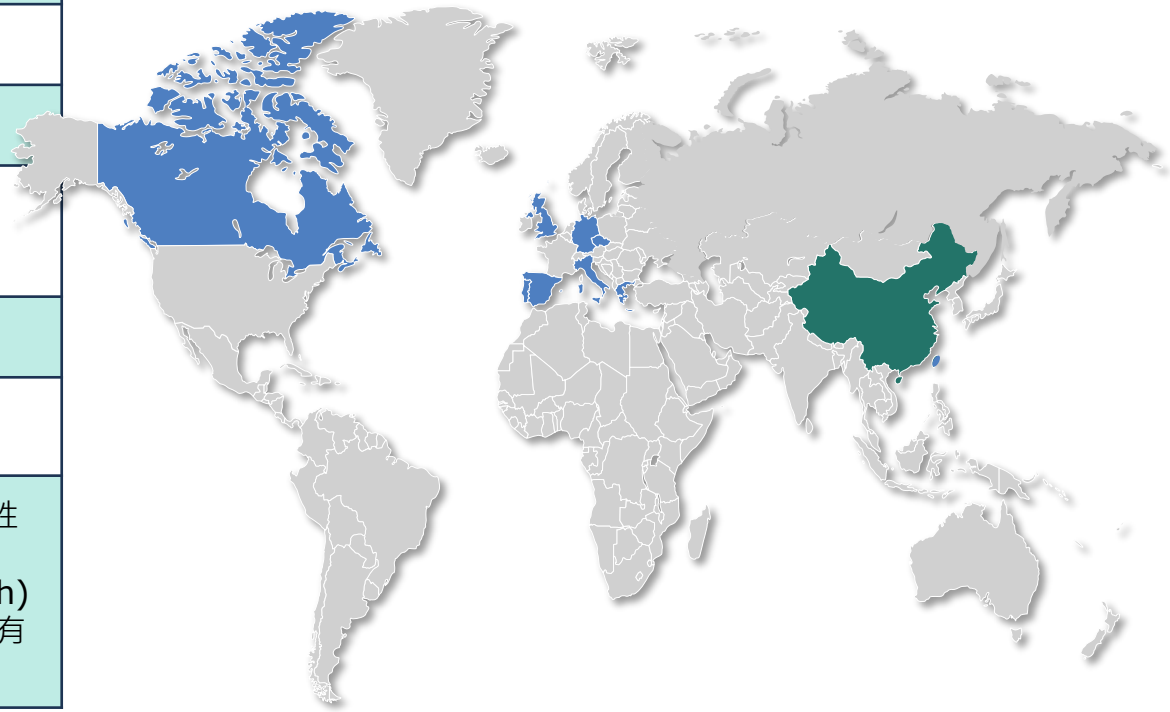
1. **Primary safety outcomes:** LT3001's six-dose, three-day regimen showed **no increased bleeding risk** in ~200 patients, meeting the primary endpoint.
2. **Secondary efficacy outcomes:**
    1) **Moderate strokes (NIHSS 7–10)** showed **+9% 90-day mRS** improvement across both doses. The high dose showed greater potential in moderate-to-severe strokes (NIHSS 11–25).
    2) In **disabling subgroups—motor drift, aphasia, and LAA**—LT3001 demonstrated additional gains of **+8–15% at day 90 mRS**, highlighting its potential to improve recovery in patients with greater neurological deficits**.**
3. **Extends treatment to 24 hours without advanced imaging**; however, findings are based on small sample sizes phase 2 study and **require confirmation in larger trials.**

LT3001 Phase 2b Program

	LT3001-202 (完成)	LT3001-205 (提早結束)
啟動中心數	34間中心 **中國**	21間中心 **美國、台灣、歐洲** (西班牙、德國、義大利、捷克、葡萄牙、希臘、英國)
目標疾病	急性缺血性中風	急性缺血性中風
治療時間窗	中風症狀發生後24小時內	中風症狀發生後24小時內
入組/目標病人數	297例/ 300例	**88例 /** 200例 (44%, 提早結束)
試驗設計	雙盲、隨機、安慰劑對照	雙盲、隨機、安慰劑對照
給藥設計	一天兩劑、連續治療三天 (共六劑)	一天兩劑、連續治療三天 (共六劑)
試驗目的	1. 多次給藥安全性 (症狀性腦出血) 2. 臨床症狀治療效果探討 3. 劑量比較 (0.05, 0.025 mg/kg)	1. 多次給藥安全性 (症狀性腦出血) 2. 影像學篩選 (mismatch) 是否有助於篩選對治療有響應病人

LT3001-205
- Patients number: **88**
- Sites activated: 21 centers in **the US, EU, UK and Taiwan**

LT3001-202
- Patients number: **297**
- Sites activated: 34 centers in **China**



LT3001-202 與 LT3001-205: 入組病人樣貌

- LT3001-205 enrolled a smaller global cohort (n=88, US/EU/Taiwan) vs. 202 in China (n=297), with later treatment (~15–17h vs. ~12h), more moderate-to-severe strokes, and inclusion of mismatch imaging.

		LT3001-202			LT3001-205	
		0.05 mg/kg	**0.025 mg/kg**	**Placebo**	**0.05 mg/kg**	**Placebo**
N		99	96	102	43	45
區域分布		China 100%			US 19%, EU 33%, Taiwan 48%	
年龄	Yrs, median (Q1, Q3)	65 (59,73)	64 (56,70)	64 (57,71)	68 (57,77)	67 (59,74)
性别	Male%	70.7%	68.8%	71.6%	67%	71%
體重	Kg, median (Q1, Q3)	68 (60,75)	70 (60,79)	70 (60,75)	72	72
发病至首次用药时间	h, median (Q1, Q3)	12.44 (11.07, 16.42)	11.81 (10.59, 19.80)	12.15 (10.77, 20.02)	15.4 (11.8, 20.0)	16.8 (10.7, 20.7)
基线NIHSS评分	median (Min, Max)	8 (4, 15)	8 (4, 16)	8 (4, 17)	7 (4, 23)	8 (4, 20)
4～6分	N (%)	25 (25.3%)	20 (20.8%)	27 (26.5%)	17 (40%)	15 (33%)
7～10分	N (%)	56 (56.6%)	55 (57.3%)	55 (53.9%)	14 (33%)	16 (36%)
11～25分	N (%)	18 (18.2%)	21 (21.9%)	20 (19.6%)	12 (27%)	14 (31%)
中風分型						
大动脉粥样硬化型 **(LAA)**	N (%)	52 (53.1%)	56 (58.3%)	61 (59.8%)		
心源性栓塞型 **(Embolic)**	N (%)	1 (1%)	2 (2.1%)	2 (2%)		
小动脉闭塞型 **(SAO)**	N (%)	44 (44.9%)	38 (39.6%)	38 (37.3%)		
其他明确病因型 **(Others)**	N (%)	0	0	0		
不明原因型 **(Unknown)**	N (%)	1 (1%)	0	1 (1%)		
Mismatch						
Yes					18 (42%)	16 (36%)

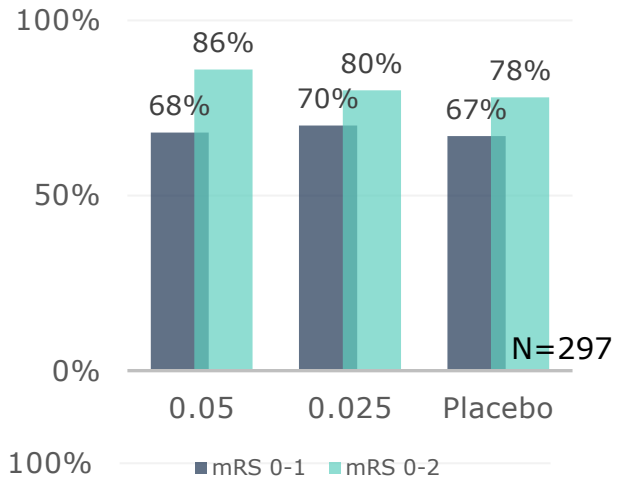
LT3001-202 與 LT3001-205: 觀察到一致性的功能改善效益

- **安全性廣泛確認，未觀察到與LT3001相關的顱內出血 (sICH):** 在兩項二期臨床試驗中皆未發生。
- **療效族群展現一致性**：中重度、失能型中風、大動脈粥狀硬化、以及 mismatch 陽性患者。
- **支持作用機制**：不僅促進血栓清除，亦能保護受威脅但仍可挽救的腦組織。
- **展現臨床價值**：特別適用於高需求患者族群，展現出顯著差異化與未滿足需求的解決方案。

202 試驗

China Phase 2

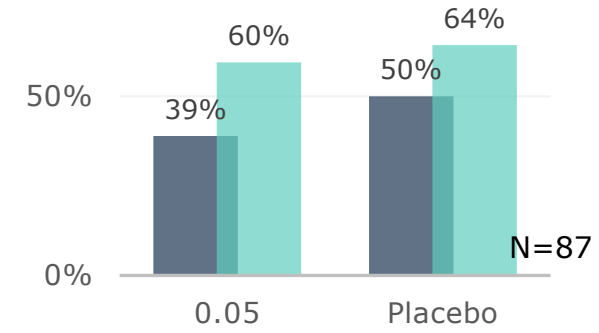
N=297



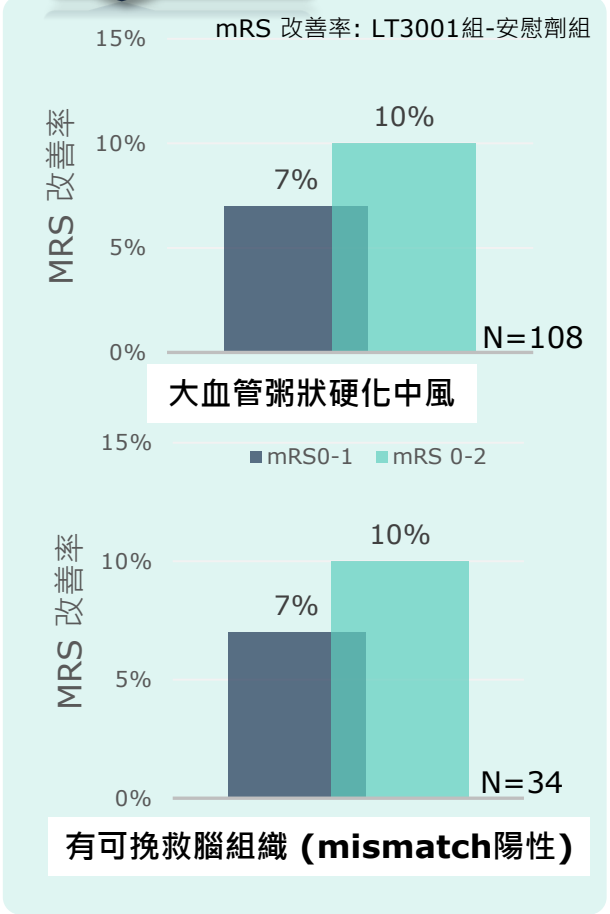
205 試驗

Global Phase 2

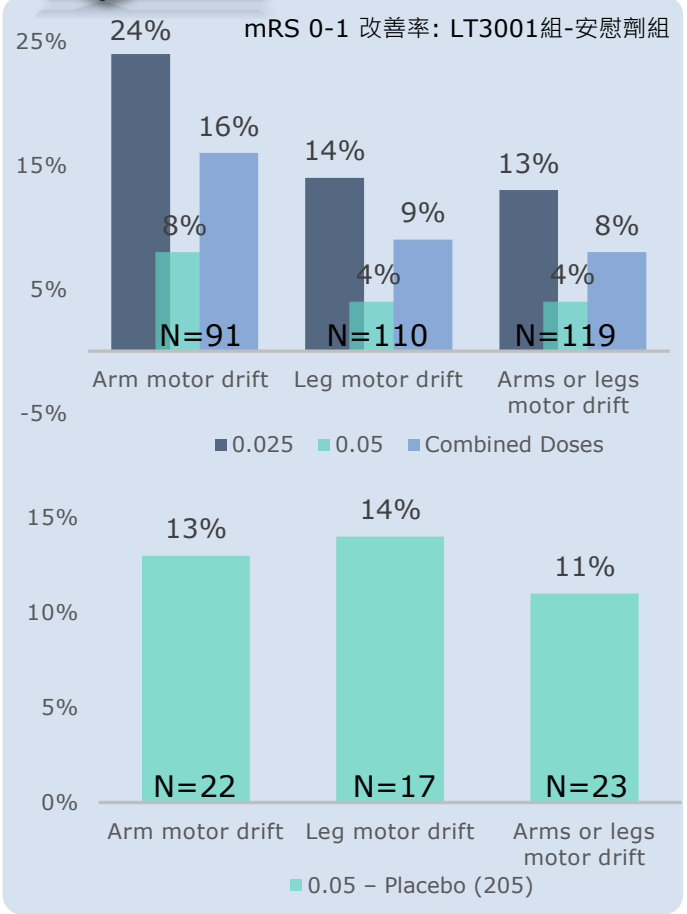
N=87 (提早結束)



影像確認中風



失能型中風



LT3001-301 臨床三期試驗設計

目標病患描述:

- **急性缺血性中風**
- 症狀發生後**24小時**內
- 無法接受tPA靜脈溶栓、無法接受器械取栓手術
- **中重度**
- **失能症狀**

隨機分派

- **LT3001** 0.025 mg/kg
- **LT3001** 0.050 mg/kg
- 安慰劑

每天二劑, 連續三天 (共治療六劑)

期中分析

- **LT3001** **最佳劑量**
- 安慰劑

總人數<1200

主要試驗終點:

90天mRS 0-2進步比率

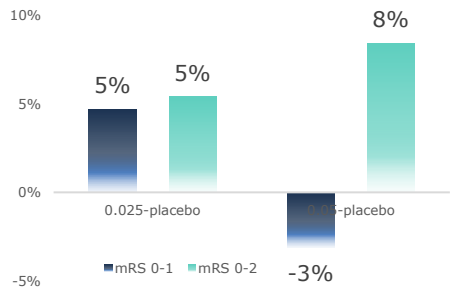
次要試驗終點:

- **mRS shift**
- **mRS 0-1**
- NIHSS response
- BI 75-100
- EQ-5D

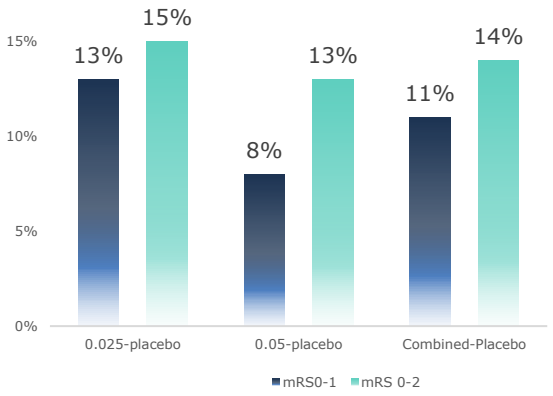
安全性終點:

- 症狀性腦出血
- 嚴重不良反應

三期樣本數計算假設:
療效Δ=8%, 需要N<1200



聚焦二期次族群分析中呈現高反應患者，以強化療效展現



LT3001 開發目標 – 效果更好、更安全 - 使用群更廣的中風新藥

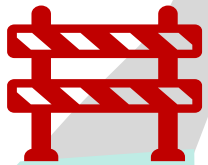
未被滿足醫療需求

急性缺血性中風的藥物治療困境 (IV tPA unmet need):

1. **腦出血副作用 (2~6%)**
2. **能使用的病人少 (<10%)**

tPA全球銷售 每年20億美金

4.5小時



LT3001的開發目標:

更安全、效果更好、嘉惠更多AIS病人

>5x時間窗、不用滿足特殊影像條件

銷售峰值60-80億美金

ACTIVASE rt-PA
– IV tPA 靜脈溶栓劑 **使用說明書**

1 INDICATIONS

ACTIVASE rt-PA (alteplase for injection) is indicated for: ①

- The management of **acute ischemic stroke** (AIS) in adults for improving neurological recovery and reducing the incidence of disability. Treatment should only be initiated within 3 hours after the onset of stroke symptoms, and after exclusion of intracranial hemorrhage by a cranial computerized tomography (CT) scan or other diagnostic imaging method sensitive for the presence of hemorrhage. Eligibility criteria of the National Institute of Neurological Disorders and Stroke (NINDS) protocol must be strictly adhered to (see 2 CONTRAINDICATIONS).

美國心臟學會 - 急性缺血性中風治療指南 (2019):

Table 8. Eligibility Recommendations for IV Alteplase in Patients With AIS

Indications (COR I)	
Within 3 h* ①	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is recommended for selected patients who may be treated within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in this table to determine patient eligibility.† (*COR I; LOE A*)
3–4.5 h* ②	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is also recommended for selected patients who can be treated within 3 and 4.5 h of ischemic stroke symptom onset or patient last known well. Physicians should review the criteria outlined in this table to determine patient eligibility.† (*COR I; LOE B-R*)§
Additional recommendations for treatment with IV alteplase for patients with AIS (COR IIa)	And (COR IIb)
Wake-up and unknown time of onset ③	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) administered within 4.5 h of stroke symptom recognition can be beneficial in patients with AIS who awake with stroke symptoms or have unclear time of onset >4.5 h from last known well or at baseline state and who have a DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR. (*COR IIa; LOE B-R*)‡

治療時間窗	接受治療需滿足的影像學條件	效果: 完全恢復 mRS=0-1		效果: 可生活自理、工作 mRS=0-2		安全: 症狀性腦出血 sICH
① **0-3 小時** (NINDS, US, 1995)	一般斷層掃描 (排除出血型中風)	tPA (n=168): 39% vs placebo (n=165): 26% (p=0.019)	**+13%**	NA		**tPA: 6.4%,** placebo: 0.6% (p<0.001)
② **3-4.5 小時** (ECASS 3, EU, 2008)		tPA (n=418): 52% vs placebo (n=403): 45% (p=0.04)	**+7%**	tPA: 66.5% vs placebo 61.5%	**+5%**	**tPA: 2.4%,** placebo: 0.2% (p=0.008)
③ **Wake-up Stroke** (WAKE-UP, EU, 2018)	核磁 MRI mismatch	tPA (n=254): 53% vs placebo (n=249): 42% (p=0.02)	**+11%**	tPA: 74% vs placebo 65%	**+9%**	**tPA: 2.4%,** placebo: 0.4% (p=0.1)
4.5-9 小時 (Extend, Australian, 2019)	斷層顯影 CTP mismatch	tPA (n=113): 35.4% vs placebo (n=112): 29.5% (p=0.04)	**+6%**	tPA:49.6% vs placebo:42.6%,	**+7%**	**tPA: 6.2%** placebo: 0.9% (p=0.053)
4.5-24 小時 LT3001	一般斷層掃描 (排除出血型中風)	**+ 11%**		**+ 14%**		**0%**

LT3001: 二期成果與三期展望

1. **安全性明確**：兩項二期試驗均未出現LT3001相關的症狀型顱內出血(sICH)，安全性獲確認。
2. **療效趨勢清晰**：在失能型中風患者中展現最顯著療效，並於大動脈粥樣硬化型及 mismatch 陽性族群分析中得到一致支持，顯示其對可救援腦組織的保護與功能恢復作用，特別有助於高醫療需求患者族群。
3. **全球三期試驗設計**：聚焦於失能型中風族群，採期中分析機制以確認劑量與調整樣本數，確保臨床效益最大化。
4. **成功機率提升**：在穩固的安全基礎與明確的療效信號支持下，結合精準的三期開發策略，**大幅提升臨床與開發成功機率**。

全球市場

歐洲每年超過90萬人口

每年新發生
缺血性中風數

美國每年超過70萬人口

每年新發生
缺血性中風數

>30%為目標中重度失能患者

缺乏治療方案、醫療負擔大

致殘第一名

造成長期嚴重殘疾的頭號原因

市場潛力

- **潛在市場大 –** 每年全球超過700萬急性缺血性中風病人, 其中又>30%為目標中重度失能患者
- **市場期待高-** 歐美市場調查顯示, 醫療專業人員開立LT3001意願高; 支付方對每例治療的價格，估計美國 25,000美元、歐洲16,000美元。
- **專利佈局完整 -** 化合物專利保護至2039年;劑型/使用方法專利延長保護至2045年

Thank you