A randomized multicenter study to determine the efficacy of sovateltide (Tycamzzi™) in patients with cerebral ischemic stroke

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Session Date: Sat, 29.10.2022
Session Time: 11:30 - 13:00
Room: Summit 1
Lecture Time: 12:25 - 12:35

Acknowledgement, Conflict and Funding Statements

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Conflict statement:

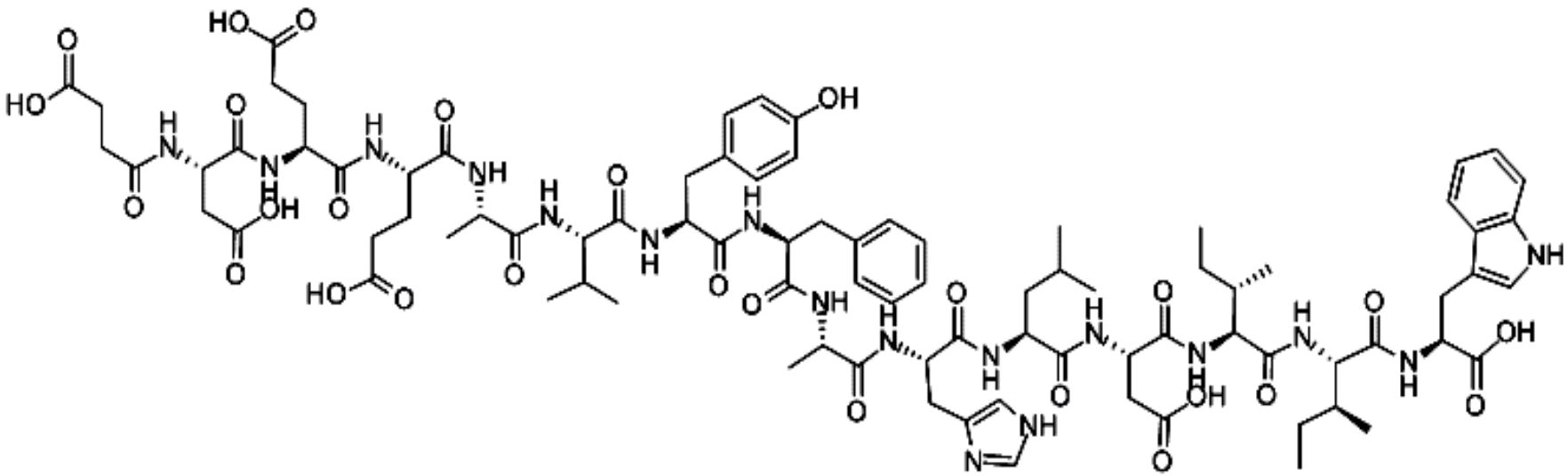
- Anil Gulati: Inventor, employee and stockholder, Pharmazz, Inc. No conflict reported by any other author.

Funding:

- Funded by Pharmazz, Inc.

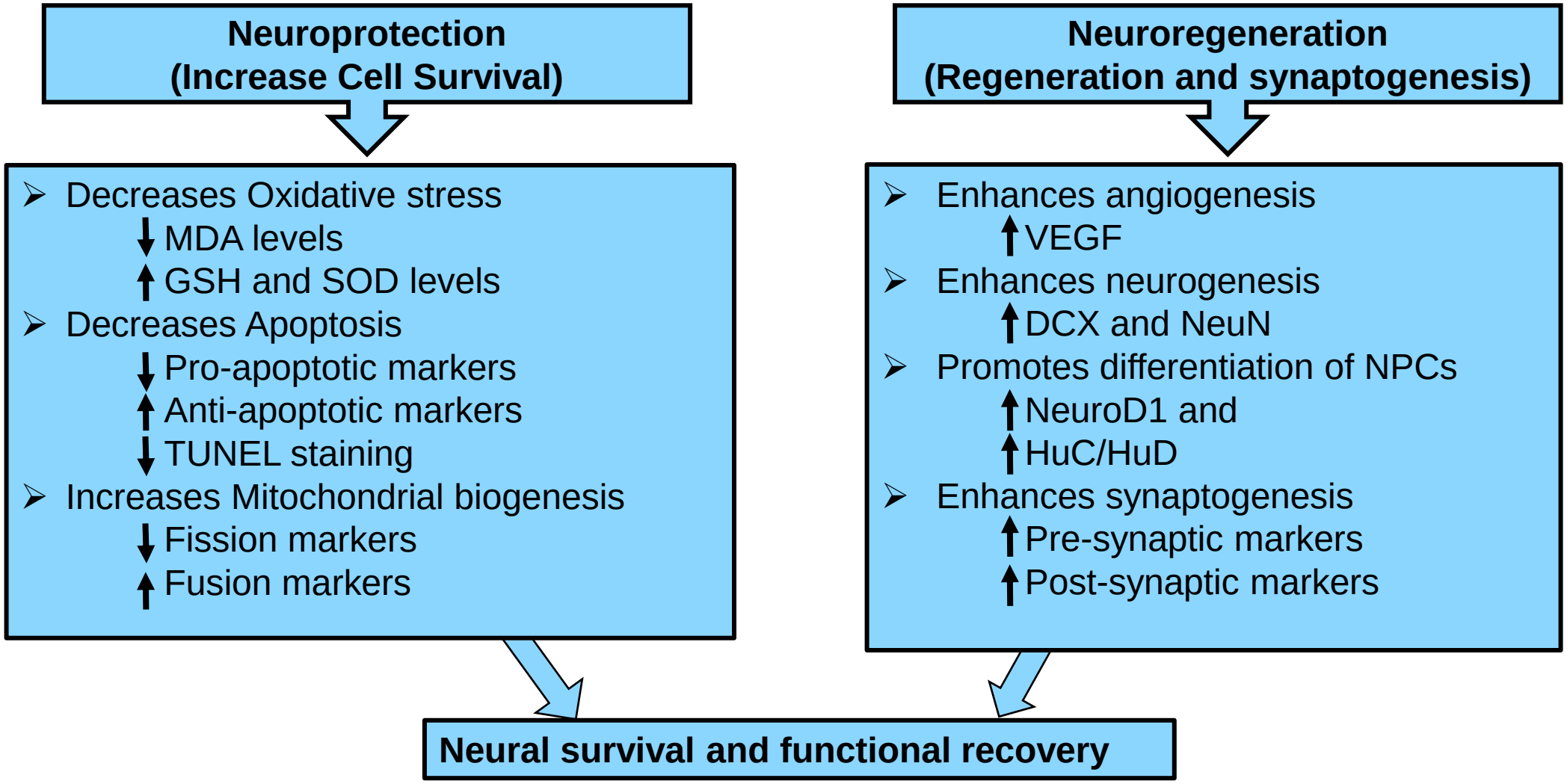
Sovateltide

Structure of Sovateltide



Other names used: IRL-1620, SPI-1620 and PMZ-1620.
International Non-proprietary Name (INN) approved by WHO is Sovateltide

Neuroprotective and Neuroregenerative Effects of Sovateltide

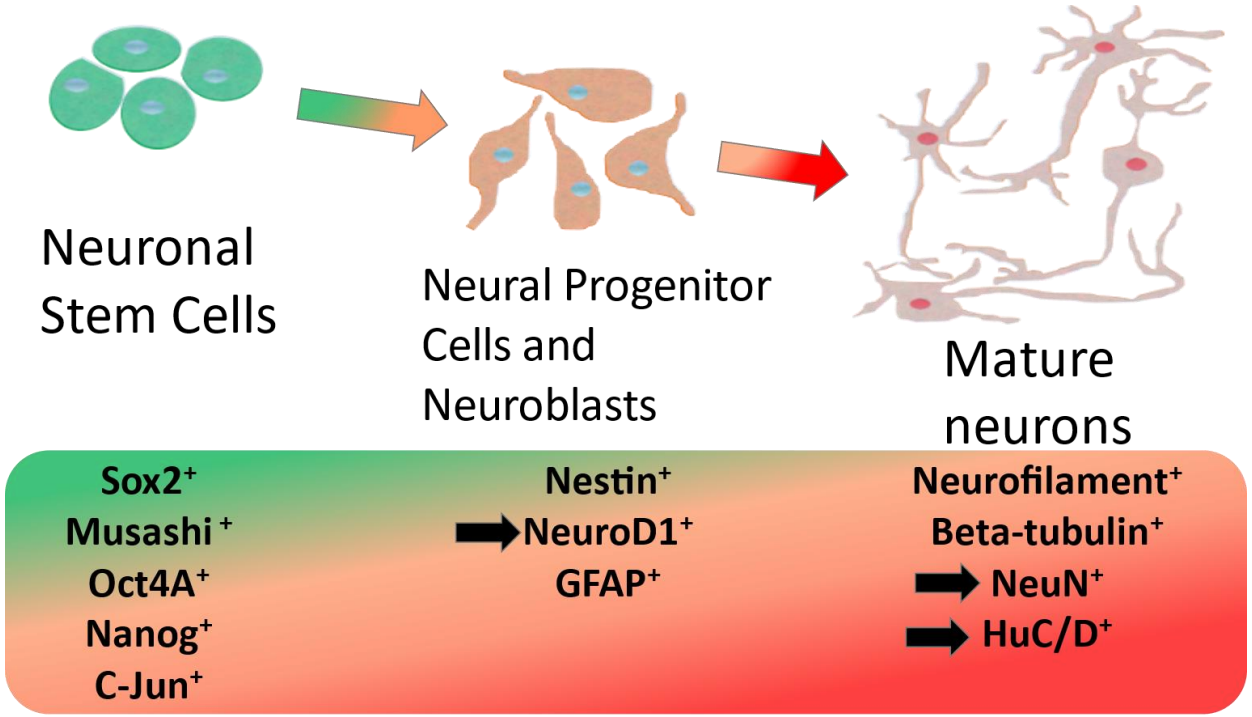


Overview of the effect of ET_B receptor agonist sovateltide on neuroprotection and neuroregeneration in cerebrovascular diseases.

Mechanism of Action

A Highly selective endothelin-B (ETB) receptor agonist

- ETB receptors in large numbers in the CNS play a key role in its development and maintenance, having a high capacity to repair the damaged brain.
- Tycamzzi™ increases vascular endothelial growth factor (VEGF) and nerve growth factor (NGF) in the brain and produces neurovascular remodeling by forming new neurons and blood vessels.
- Tycamzzi™ has anti-apoptotic activity and protects neural mitochondria, and enhances their biogenesis
- Significantly reduces infarct volume and improves neurological outcomes in an animal model of ACIS*
- Clinically, sovateltide was found to be safe, well-tolerated, and improved neurological outcomes**



Sovateltide enhances the expression of markers for neural progenitor cells and neuronal cells, but not the stem cell markers. The likely site of action is the neural progenitor cells.

Ranjan et al., Sci Rep. 2020 Jul 29;10(1):12737. PMID: 32728189
Ranjan et al., Can J Physiol Pharmacol. 2020 Sep;98(9):659-666. PMID: 32574518
Briyal et al., Sci Rep. 2019 Jul 18;9(1):10439. PMID: 31320660
*Leonard et al., Brain Res. 2011;1420:48–58; Brain Res. 2012;1464:14–23; Brain Res. 2013;1528:28–41; Gulati Curr. Neuropharmacol. 2016;14(6):619–26
**Gulati et al., (2021) CNS Drugs 35; 85–104. PMID: 33428177; https://rdcu.be/cdps6

Phase II Results

Sovateltide was safe and well-tolerated and resulted in improved neurological outcomes in patients with acute cerebral ischemic stroke 90 days post-treatment.

CNS Drugs (2021) 35:85–104
https://doi.org/10.1007/s40263-020-00783-9

ORIGINAL RESEARCH ARTICLE

Check for updates

Safety and Efficacy of Sovateltide (IRL-1620) in a Multicenter Randomized Controlled Clinical Trial in Patients with Acute Cerebral Ischemic Stroke

Anil Gulati[1,2] · Nilesh Agrawal[3] · Deepti Vibha[4] · U. K. Misra[5] · Birinder Paul[6] · Dinesh Jain[6] · Jeyaraj Pandian[7] · Rupam Borgohain[8]

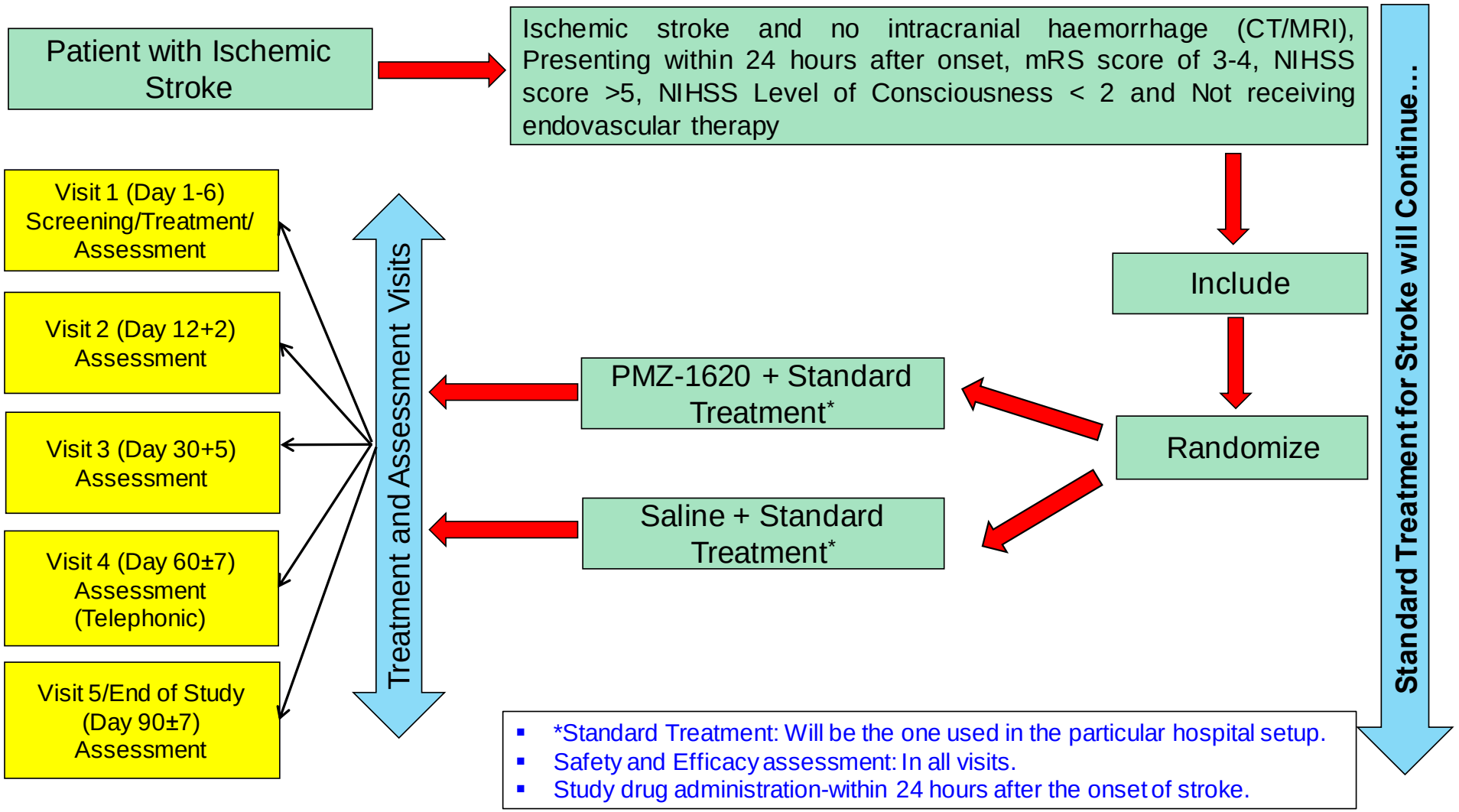
Sovateltide

Phase III Trial Sites (58.2% patients enrolled at sites with at least 40 ICU beds)

S. No.	Name and Address of the Site (Country: India)	Total Beds	ICU Beds
1	Radiant Superspeciality Hospital, Sabnis Plot, Kalyan Nagar Square, Amravati 444606, Maharashtra.	45	14
2	Pushpanjali Hospital & Research Centre Pvt. Ltd. Pushpanjali Palace, Delhi Gate, Agra 282002, Uttar Pradesh.	195	40
3	New Era Hospital, Queta Colony, Near Telephone Exchange Square, Central Avenue Road, Nagpur 440008, Maharashtra.	60	20
4	Lalitha Super Specialties Hospital Pvt. Ltd., Kothapet, Guntur 522001, Andhra Pradesh.	300	100
5	Christian Medical College & Hospital, Department of Neurology, Brown Road, Ludhiana 141008, Punjab.	840	60
6	Dayanand Medical College and Hospital, Department of Neurology, Civil Lines, Tagore Nagar, Ludhiana 141001, Punjab.	1326	157
7	KLE's Dr. Prabhakar Kore Hospital & Medical Research Centre, Nehru Nagar Belagavi 590010, Karnataka.	2400	250
8	Sidhu Hospital Pvt. Ltd. G.T. Road, Doraha, Ludhiana 141421, Punjab.	130	20
9	Heritage Institute of Medical Sciences, NH-2 (GT Road Bypass), Varanasi 221311, Uttar Pradesh.	550	20
10	All India Institute of Medical Sciences, Department of Neurology, Neurosciences Center, Ansari Nagar, New Delhi 110029.	2362	86
11	Institute of Neurosciences, Department of Neurology, 185/1, A. J. C. Bose Road, Kolkata 700017, West Bengal.	1360	32
12	Guntur Medical College & Government General Hospital, Department of Neurology, Podila Prasad Super Specialty, Block III Floor, Guntur 522001, Andhra Pradesh.	1170	250
13	Post Graduate Institute of Medical Education & Research, Department of Neurology, Ground Floor, Block-A, Nehru Hospital, Sector-12, Chandigarh 160012.	2200	250
14	Baby Memorial Hospital, Indira Gandhi Road, Kozhikode 673004, Kerala.	800	200
15	Government Medical College and Attached Hospitals, Department of Neurology, MBS Hospital, Rangbari Road, Kota 324002 Rajasthan.	1200	150
16	Hi-Tech Hospital and Trauma Center, Opposite MLB Medical College, Gate No.4, Kanpur Road, Jhansi 284128, Uttar Pradesh.	20	7
17	Institute of Medical Sciences, Department of Neurology, Banaras Hindu University, Varanasi 221005, Uttar Pradesh.	2000	70
18	KG Hospital and Post Graduate Medical Institute, Door No-5, Arts College Road, Coimbatore 641018, Tamil Nadu.	250	45

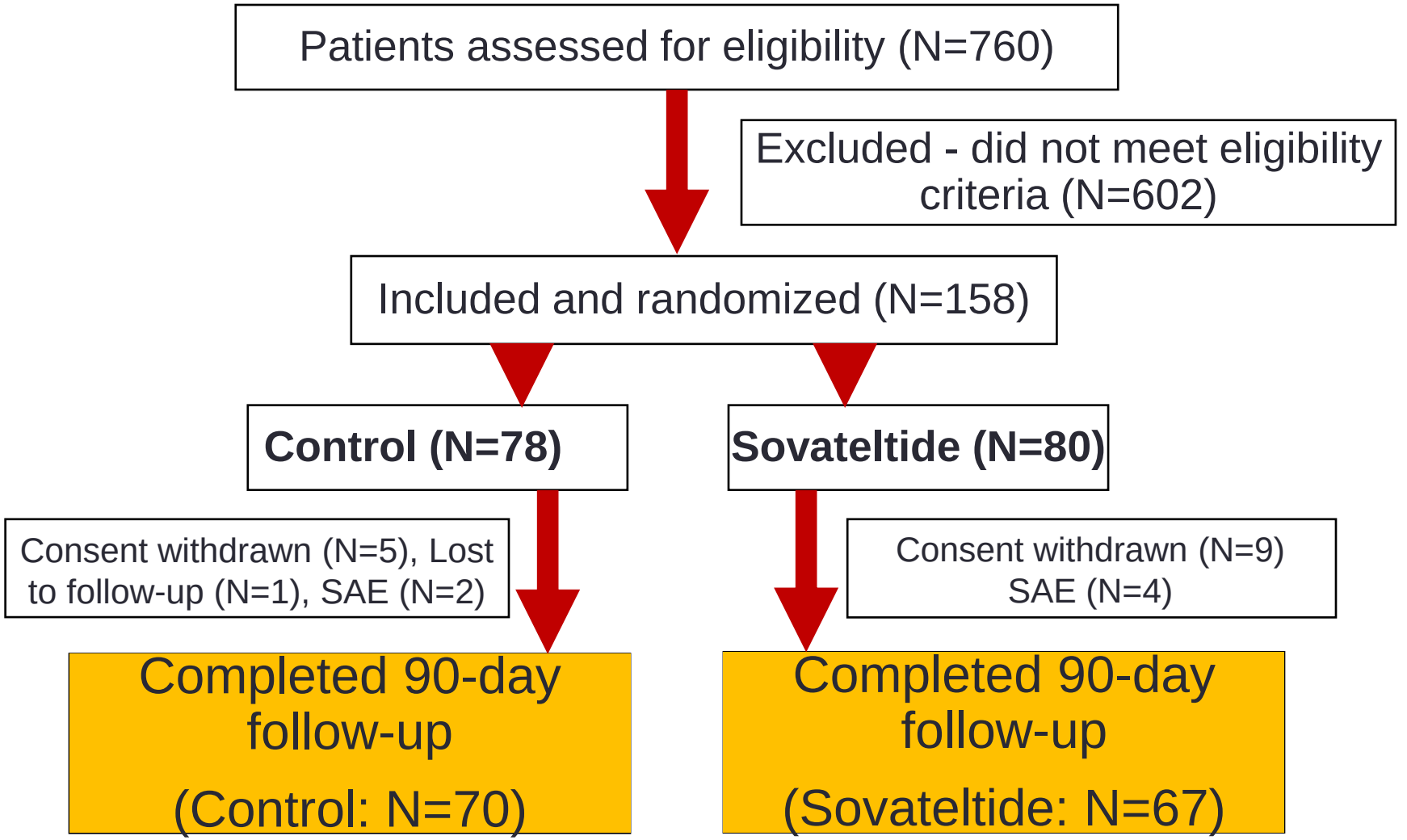
Sovateltide

Clinical Phase III Trial Design



Sovateltide (Tycamzzi™) Phase III Study: Subject Recruitment

Conducted in 18 centers, 58.2 % patients enrolled from 12 sites having more than 300 beds with at least 40 ICU beds



Several centers have participated in global clinical trials (results published in high impact journals)

Sovateltide

Phase III Patient Demographics

Variable	Sovateltide (N=80)	Control (N=78)
Mean Age (years)	55.78	59.27
Mean Body Weight (Kg)	65.75	65.56
Male Sex (number, %)	53, 66.2%	48, 61.5%
Median NIHSS at Baseline (IQR)	9 (7 to 12)	10 (8 to 13)
Median ASPECTS (IQR)	8 (7 to 9)	8 (7 to 9)
Thrombolytic Therapy (number, %)	9, 11.2%	20, 25.6%
Large Artery Atherosclerosis (number, %)	37, 46.25%	29, 37.17%
Median Interval (hours) between of stroke onset and treatment (IQR)	18.58 (11.8 to 23.1)	19.71 (12.4 to 23.3)

IQR=Interquartile range

Details of Stroke Sub-types

S. No.	Stroke Sub-Types	Saline (N=78)	Sovateltide (N=80)
1	Large Artery Atherosclerosis	29 (37.17%)	37 (46.25%)
2	Cardioembolism	11 (14.10%)	5 (6.25%)
3	Small Vessel Occlusion	29 (37.17%)	29 (36.25%)
4	Stroke of other Determined Etiology	2 (2.56%)	0 (0.00%)
5	Stroke of Undetermined Etiology	7 (8.97%)	9 (11.25%)

Sovateltide

Phase III Results (Primary endpoint)

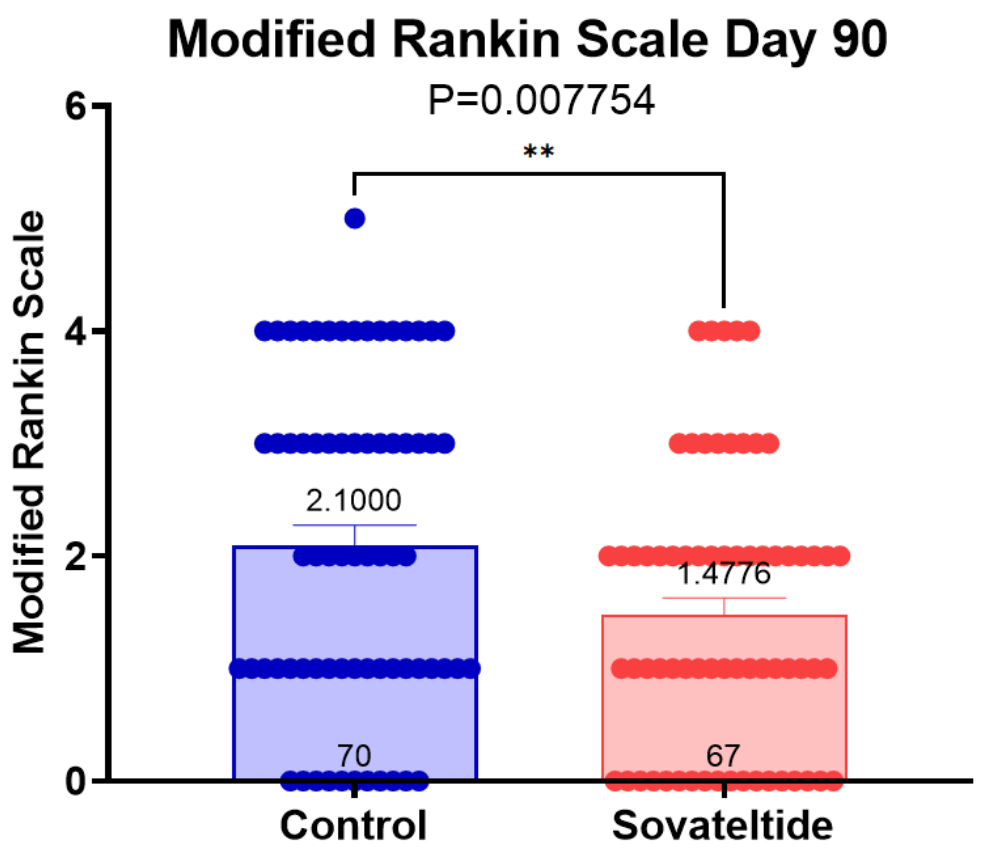


Table Analyzed	Modified Rankin Scale Control vs Sovateltide Day 90
Column B	Sovateltide
vs.	vs.
Column A	Control
Unpaired t test	
P value	0.0078
One- or two-tailed P value?	Two-tailed
t, df	t=2.703, df=135
Mean of column A	2.100
Mean of column B	1.478
Difference between means (B - A) ± SEM	-0.6224 ± 0.2303
95% confidence interval	-1.078 to -0.1670
F, DFn, Dfd	1.418, 69, 66
Sample size, column A	70
Sample size, column B	67

Sovateltide

Phase III Results (Primary endpoint)

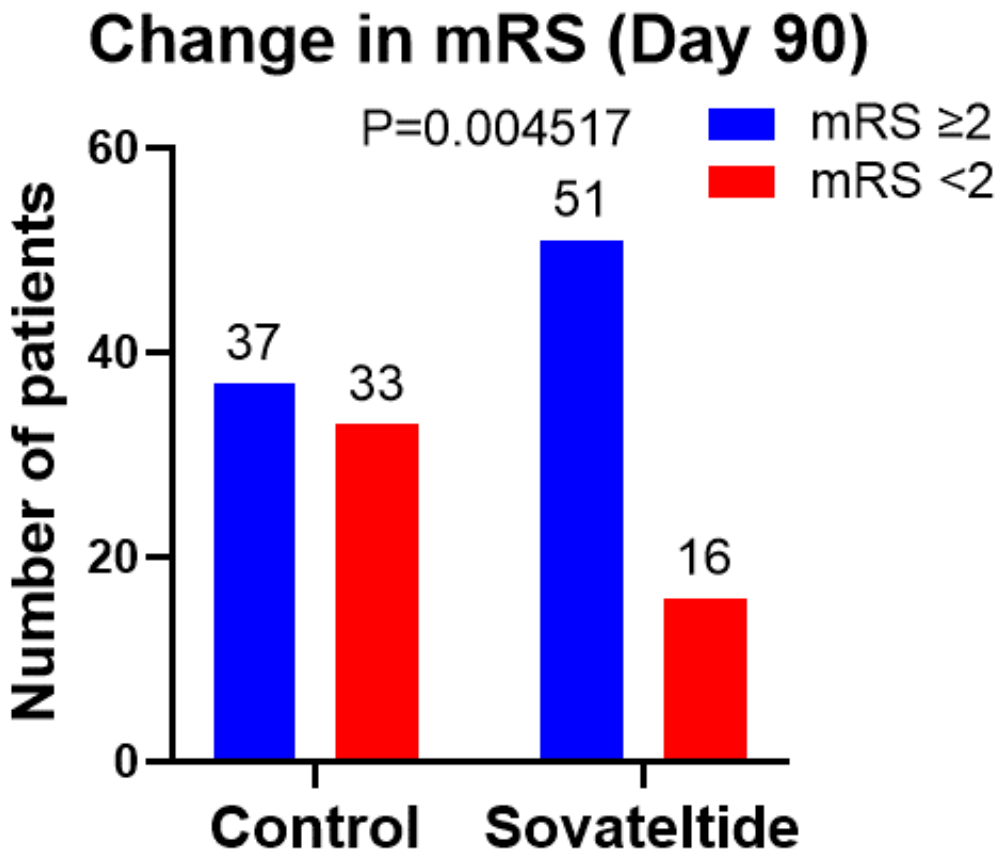


Table Analyzed	Change in mRS of 2 or more from day 1 to day 90
Test	Chi-square
Chi-square, df	8.063, 1
z	2.840
P value	0.0045
Odds ratio	2.843
95% confidence interval	1.368 to 6.015
Control	52.86%
Sovateltide	76.12%
Sample size, column A	70
Sample size, column B	67

Sovateltide

Phase III Results (Primary endpoint)

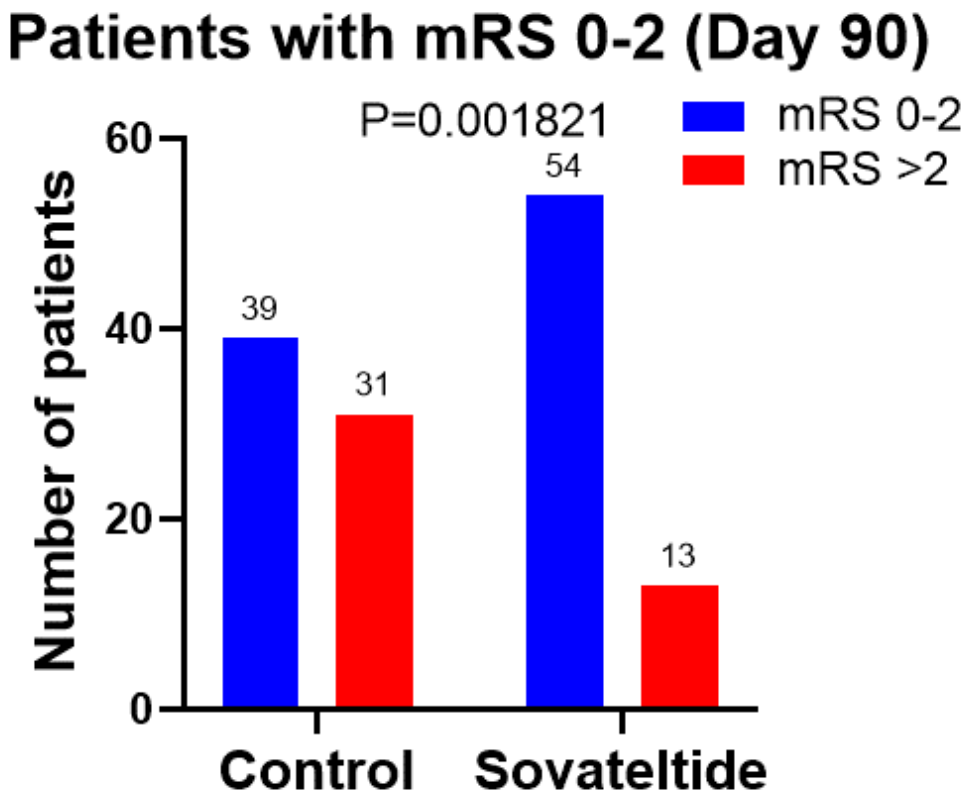


Table Analyzed	Number of patients with mRS of 2 or less at day 90
Test	Chi-square
Chi-square, df	9.722, 1
z	3.118
P value	0.0018
Odds ratio	3.302
95% confidence interval	1.501 to 7.044
Control	55.71%
Sovateltide	80.60%
Sample size, column A	70
Sample size, column B	67

Sovateltide

Phase III Results (Primary endpoint)

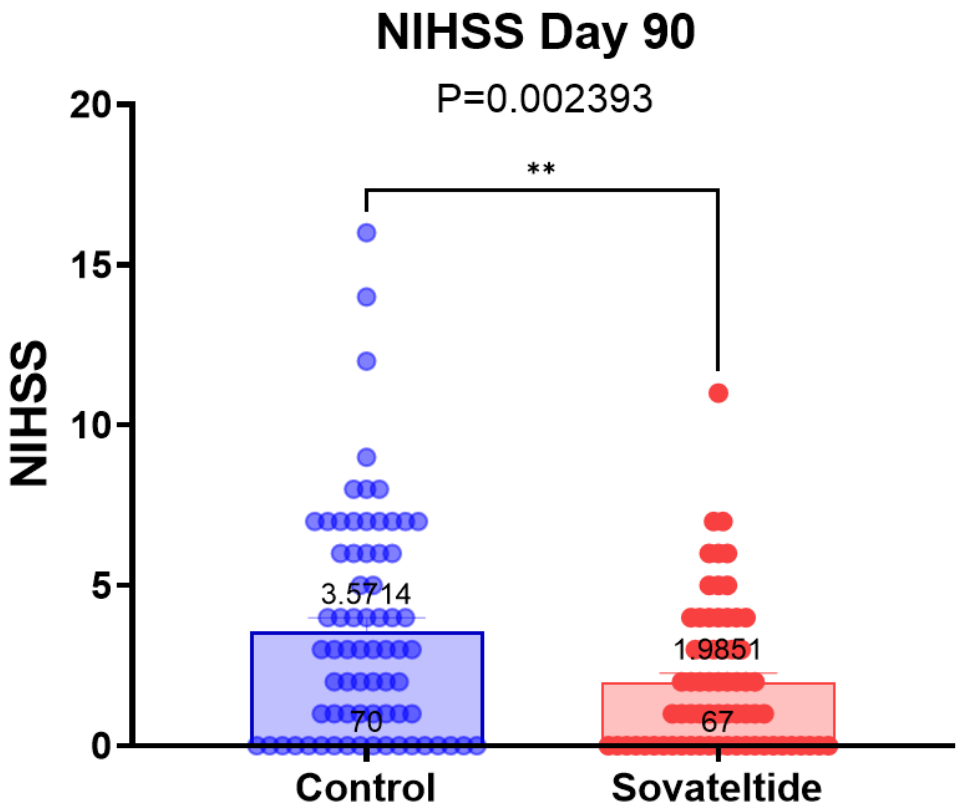


Table Analyzed	NIHSS Control vs Sovateltide Day 90
Column B	Sovateltide
vs.	vs.
Column A	Control
Unpaired t test	
P value	0.0024
One- or two-tailed P value?	Two-tailed
t, df	t=3.095, df=135
Mean of column A	3.571
Mean of column B	1.985
Difference between means (B - A) ± SEM	-1.586 ± 0.5126
95% confidence interval	-2.600 to -0.5727
F, DFn, Dfd	2.352, 69, 66
Sample size, column A	70
Sample size, column B	67

Sovateltide

Phase III Results (Primary endpoint)

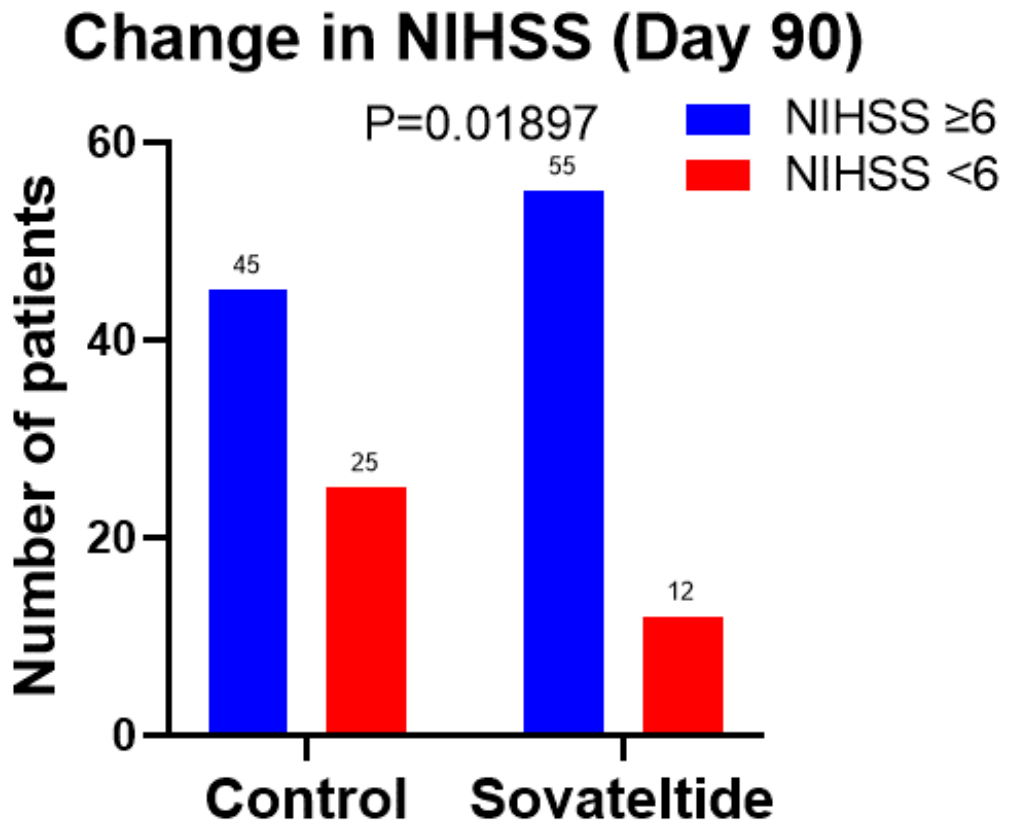


Table Analyzed	Change in NIHSS of 6 or more from day 1 to day 90
Test	Chi-square
Chi-square, df	5.505, 1
z	2.346
P value	0.0190
Odds ratio	2.546
95% confidence interval	1.176 to 5.798
Control	64.29%
Sovateltide	82.09%
Sample size, column A	70
Sample size, column B	67

Sovateltide

Phase III Results (Primary endpoint)

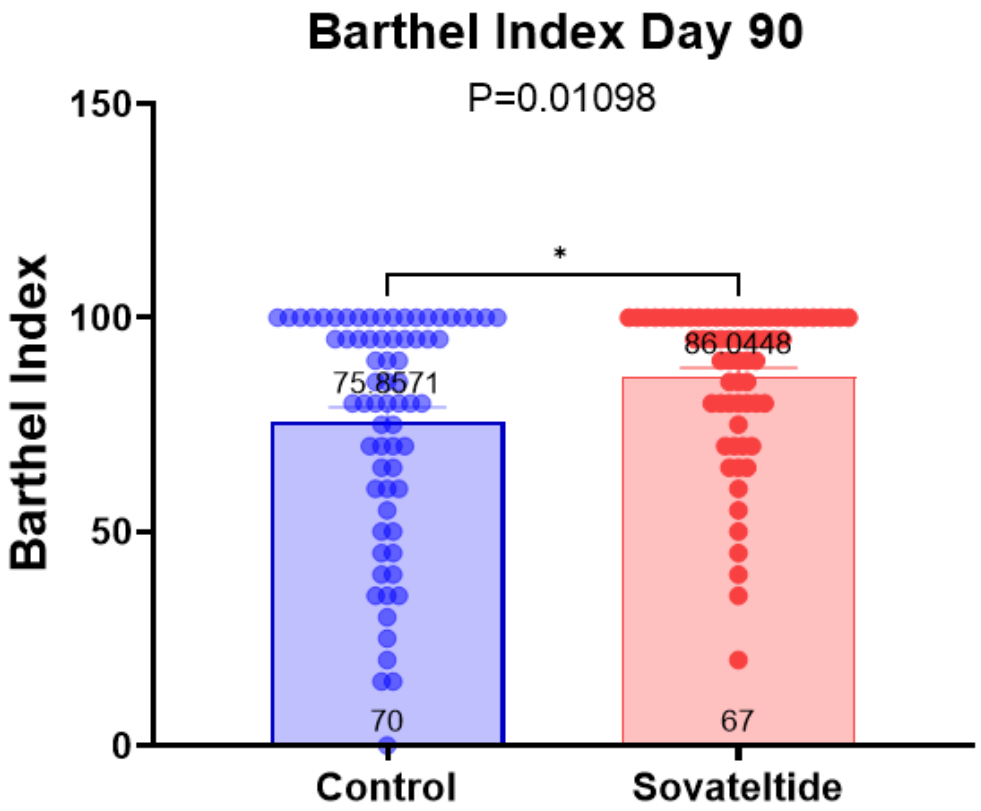


Table Analyzed	Barthel Index Control vs Sovateltide Day 90
Column B	Sovateltide
vs.	vs.
Column A	Control
Unpaired t test	
P value	0.0110
One- or two-tailed P value?	Two-tailed
t, df	t=2.579, df=135
Mean of column A	75.86
Mean of column B	86.04
Difference between means (B - A) ± SEM	10.19 ± 3.950
95% confidence interval	2.375 to 18.00
F, DFn, Dfd	2.113, 69, 66
Sample size, column A	70
Sample size, column B	67

Sovateltide

Phase III Results (Primary endpoint)

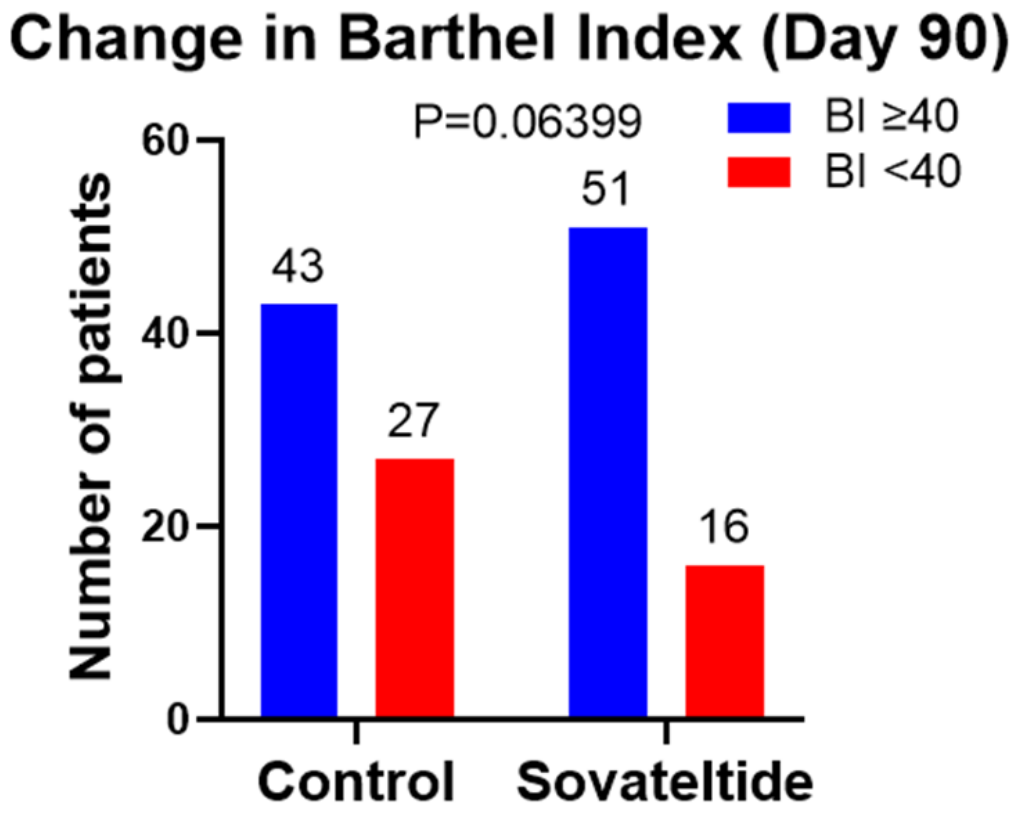
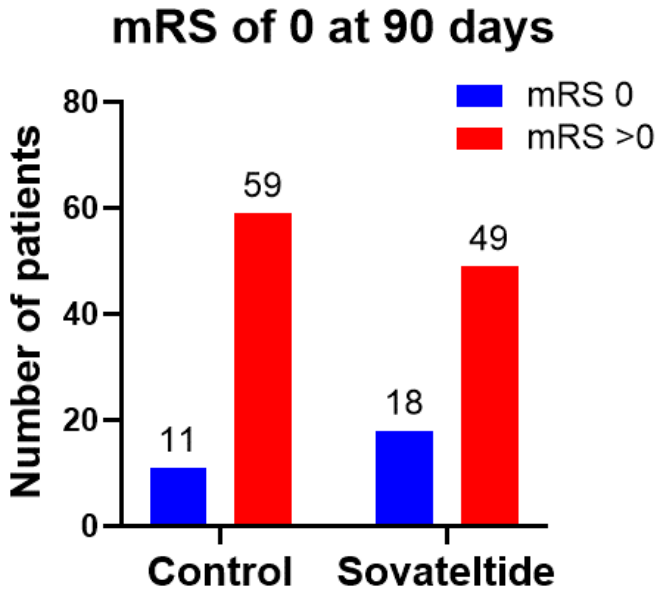


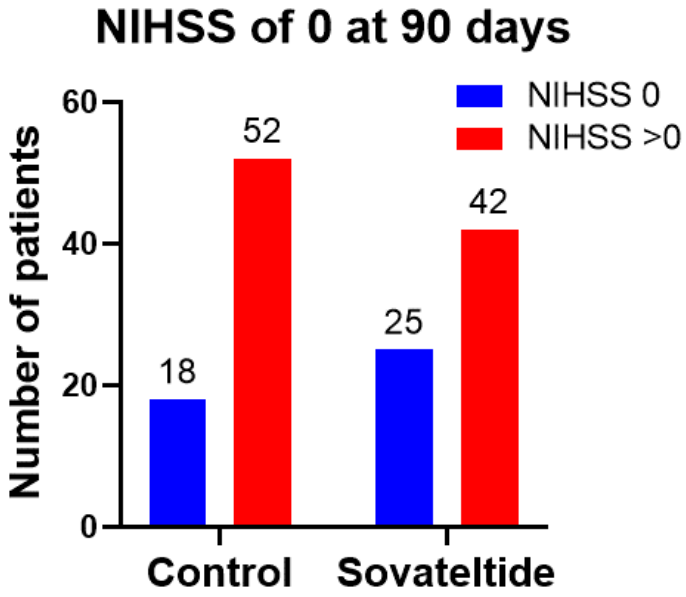
Table Analyzed	Change in BI of 40 or more from day 1 to day 90
Test	Chi-square
Chi-square, df	3.431, 1
z	1.852
P value	0.0640
Odds ratio	2.001
95% confidence interval	0.9385 to 4.276
Control	61.43%
Sovateltide	76.12%
Sample size, column A	70
Sample size, column B	67

Sovateltide

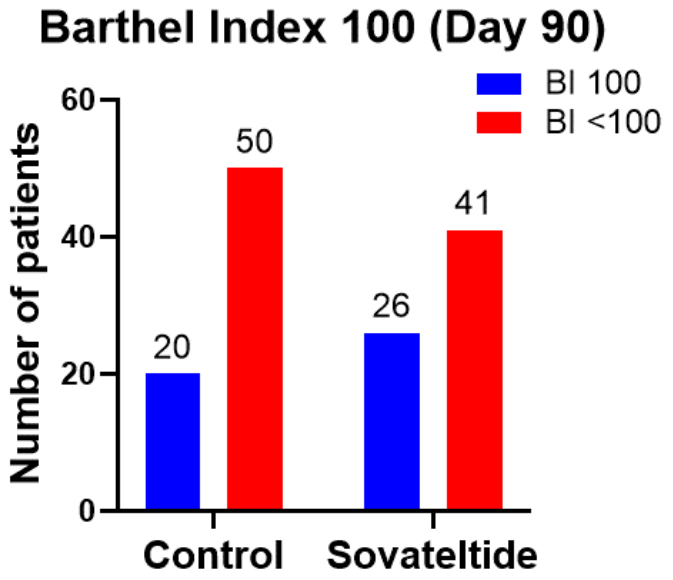
Phase III Results (Exploratory endpoint)



Group	mRS 0	mRS >0
Control	15.71%	84.29%
Sovateltide	26.87%	73.13%



Group	NIHSS 0	NIHSS >0
Control	25.71%	74.29%
Sovateltide	37.31%	62.69%



Group	BI 100	BI <100
Control	28.57%	71.43%
Sovateltide	38.81%	61.19%

Sovateltide

Phase III Results (Secondary endpoint)

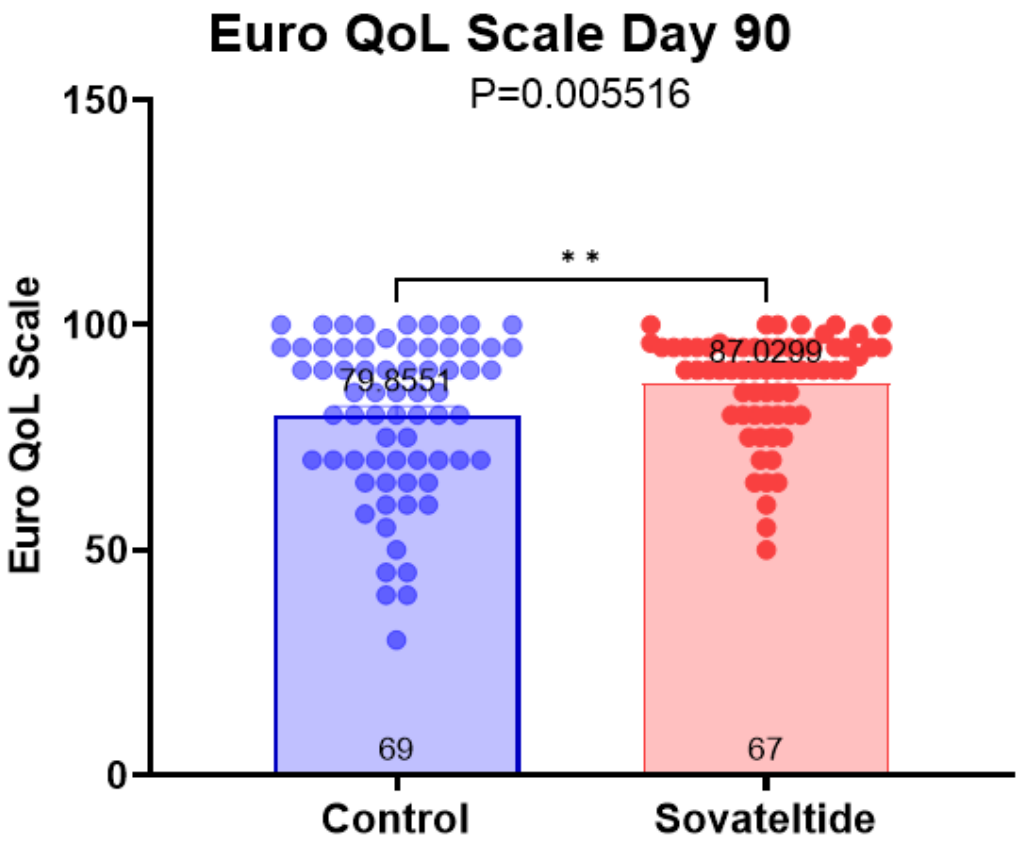


Table Analyzed	Euro QoL Scale EQ-5D-5L Control vs Sovateltide Day 90
Column B	Sovateltide
vs.	vs.
Column A	Control
Unpaired t test	
P value	0.0055
One- or two-tailed P value?	Two-tailed
t, df	t=2.821, df=134
Mean of column A	79.86
Mean of column B	87.03
Difference between means (B - A) ± SEM	7.175 ± 2.543
95% confidence interval	2.144 to 12.21
F, DFn, Dfd	2.291, 68, 66
Sample size, column A	69
Sample size, column B	67

Sovateltide

Phase III Results (Secondary endpoint)

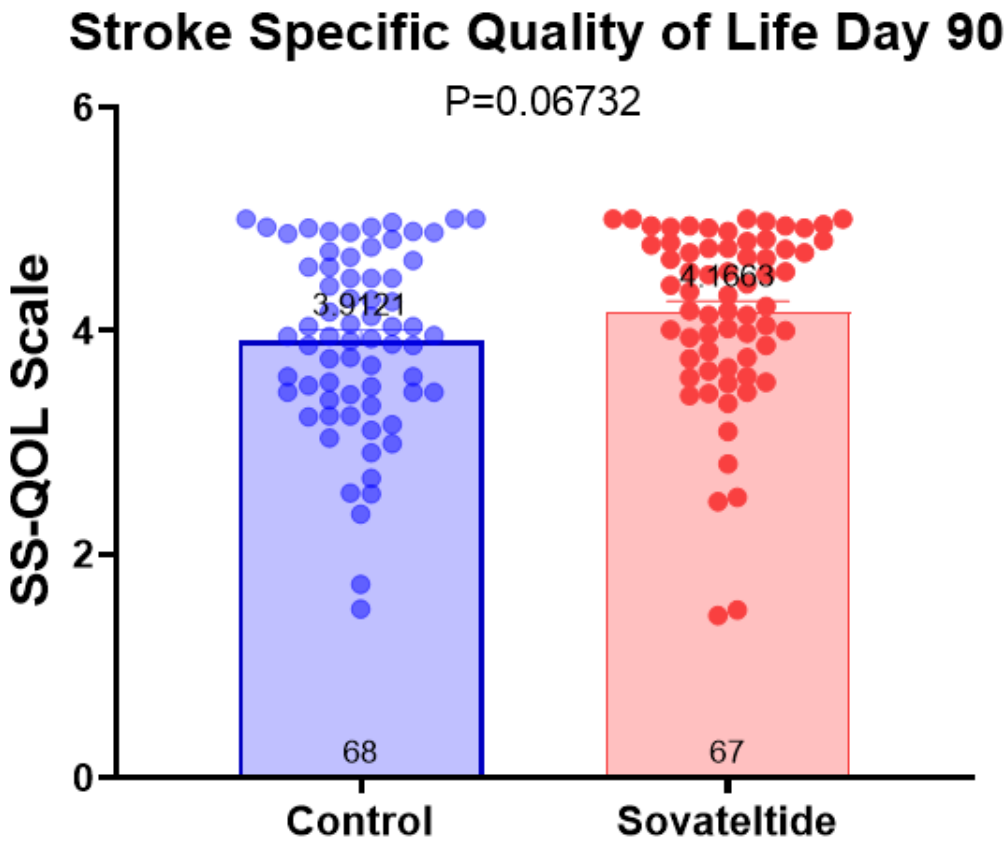


Table Analyzed	SS-QOL Control vs Sovateltide Day 90
Column B	Sovateltide
vs.	vs.
Column A	Control
Unpaired t test	
P value	0.0673
One- or two-tailed P value?	Two-tailed
t, df	t=1.845, df=133
Mean of column A	3.912
Mean of column B	4.166
Difference between means (B - A) ± SEM	0.2542 ± 0.1378
95% confidence interval	-0.01838 to 0.5268
F, DFn, Dfd	1.050, 67, 66
Sample size, column A	68
Sample size, column B	67

Sovateltide

Phase III Results (Secondary endpoint)

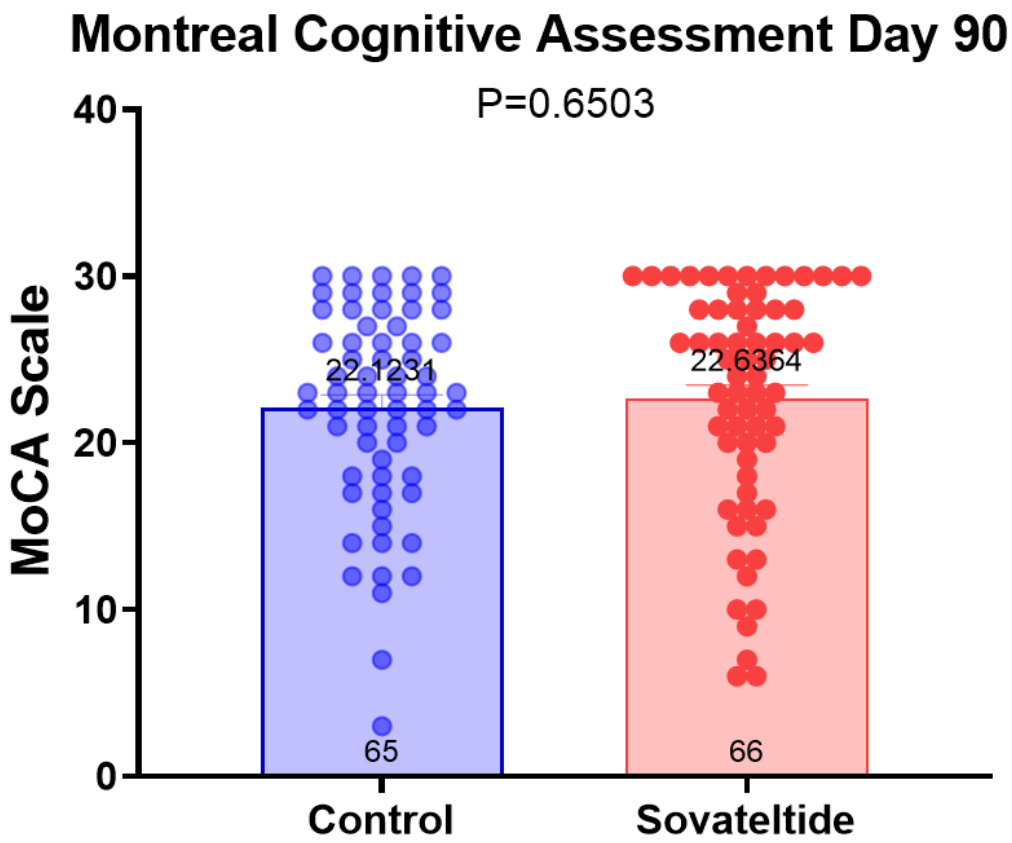
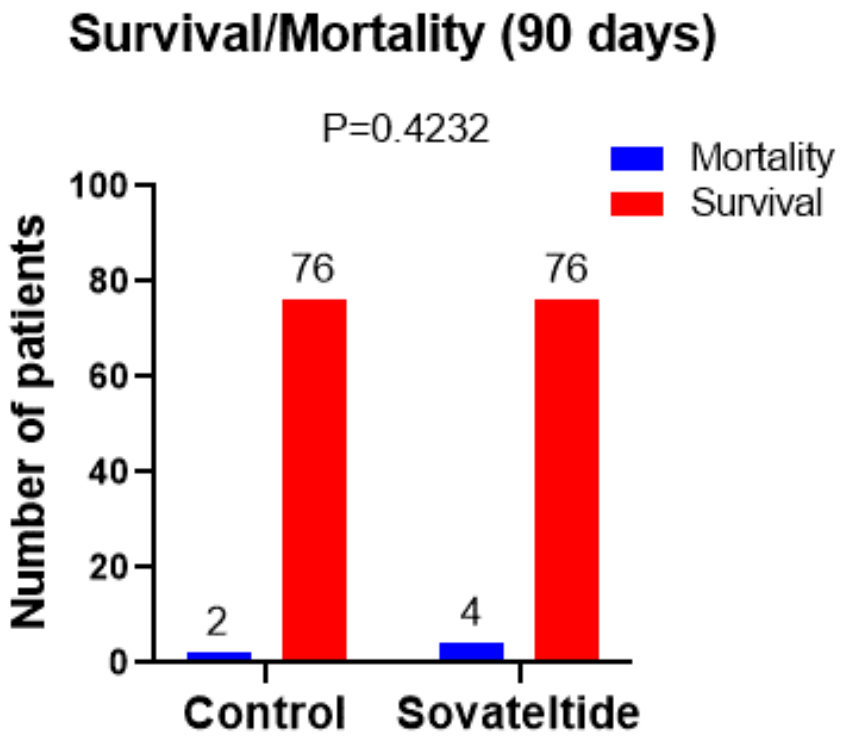
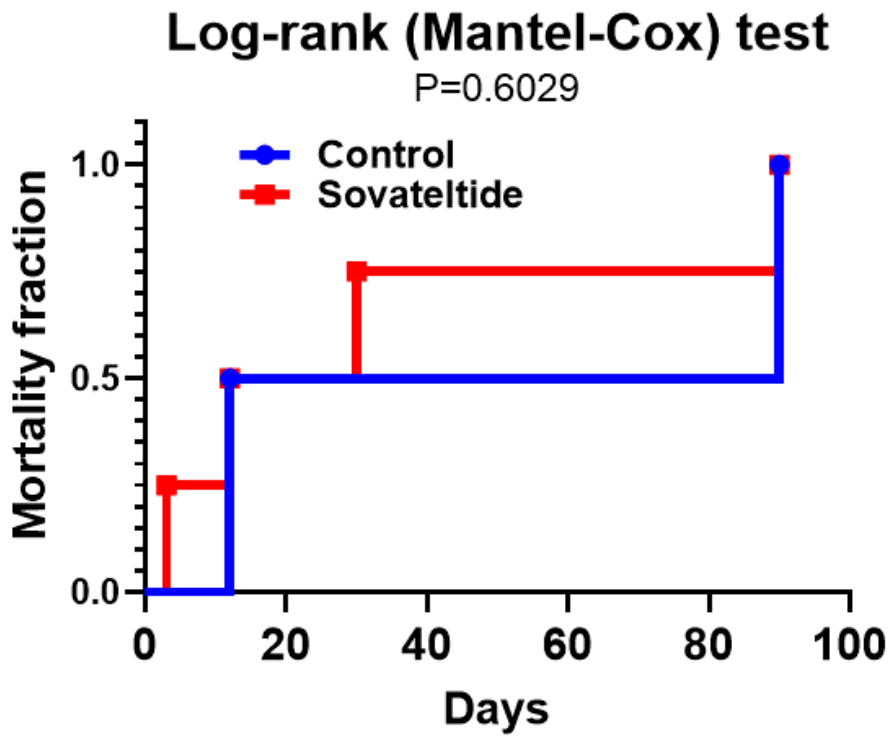


Table Analyzed	MoCA Control vs Sovateltide Day 90
Column B	Sovateltide
vs.	vs.
Column A	Control
Unpaired t test	
P value	0.6503
One- or two-tailed P value?	Two-tailed
t, df	t=0.4544, df=129
Mean of column A	22.12
Mean of column B	22.64
Difference between means (B - A) ± SEM	0.5133 ± 1.130
95% confidence interval	-1.722 to 2.748
F, DFn, Dfd	1.273, 65, 64
Sample size, column A	65
Sample size, column B	66

Sovateltide

Phase III Results (Adverse events)



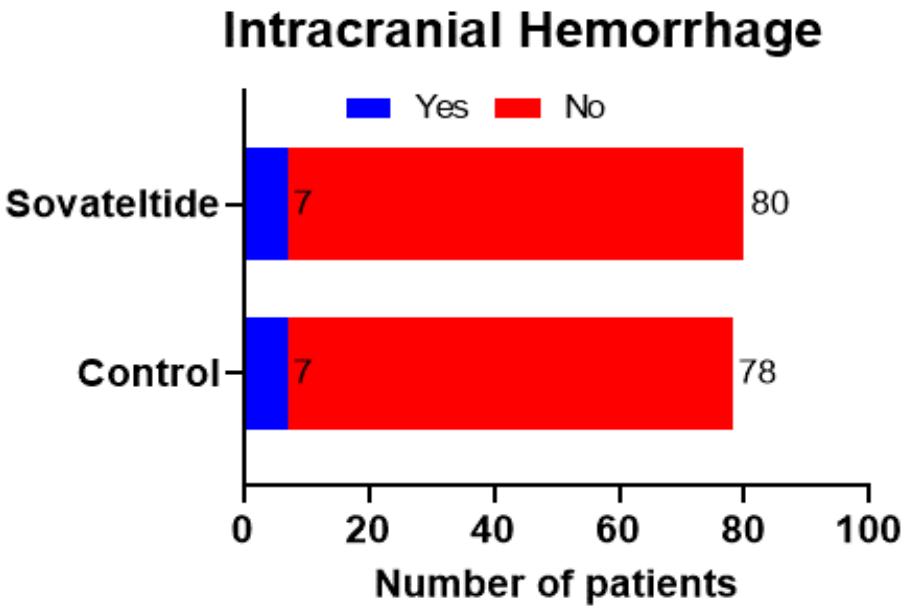


Stroke Subtype	Control	Sovateltide
Large artery atherosclerosis	1	3
Small vessel occlusion	1	1

Sovateltide

Phase III Results (Adverse events)

	Saline (N=78) 33 adverse events in 24 patients	Sovateltide (N=80) 27 adverse events in 15 patients
Serious	**2 events in 2 patients** ▪ Death (2)	**5 events in 5 patients** ▪ Death (4) ▪ Hyponatremia (1)
Moderate	**22 events in 16 patients** ▪ Fever (5 events in 2 patients) ▪ Hypertension (2 events in 2 patients) ▪ Cold (2 events in 2 patients) ▪ Headache (1) ▪ Cough (1) ▪ Pruritus (1) ▪ Vomiting (1) ▪ Hepatitis (1) ▪ Hypocalcemia (1) ▪ Hypokalemia (1) ▪ Hypotension (1) ▪ Lower respiratory tract infection (1) ▪ Urinary tract infection (1) ▪ Constipation (1) ▪ Itching (1) ▪ Body pain (1)	**19 events in 7 patients** ▪ Hypertension (3 events in 3 patients) ▪ Vomiting (2 events in 2 patients) ▪ Dizziness (2 events in 2 patients) ▪ Breathlessness (1) ▪ Cough (1) ▪ Headache (1) ▪ Hypotension (1) ▪ Tachypnoea (1) ▪ Rash (1) ▪ Urinary Incontinence (1) ▪ Sepsis (1) ▪ Septic shock (1) ▪ Fever (1) ▪ Increased Alkaline Phosphatase (1) ▪ Depression (1)
Mild	**9 events in 6 patients** ▪ Abdominal pain (3 events in 3 patients) ▪ Fever (1) ▪ Headache (1) ▪ Cough (1) ▪ Sclera discoloration (1) ▪ Burning sensation in feet (1) ▪ Facial & pedal edema (1)	**3 events in 3 patients** ▪ Dyspnea (1) ▪ Chills (1) ▪ Back pain (1)



Chi-square, df	0.002462, 1
Control	8.97%
Sovateltide	8.75%
P value	0.9604

Sovateltide

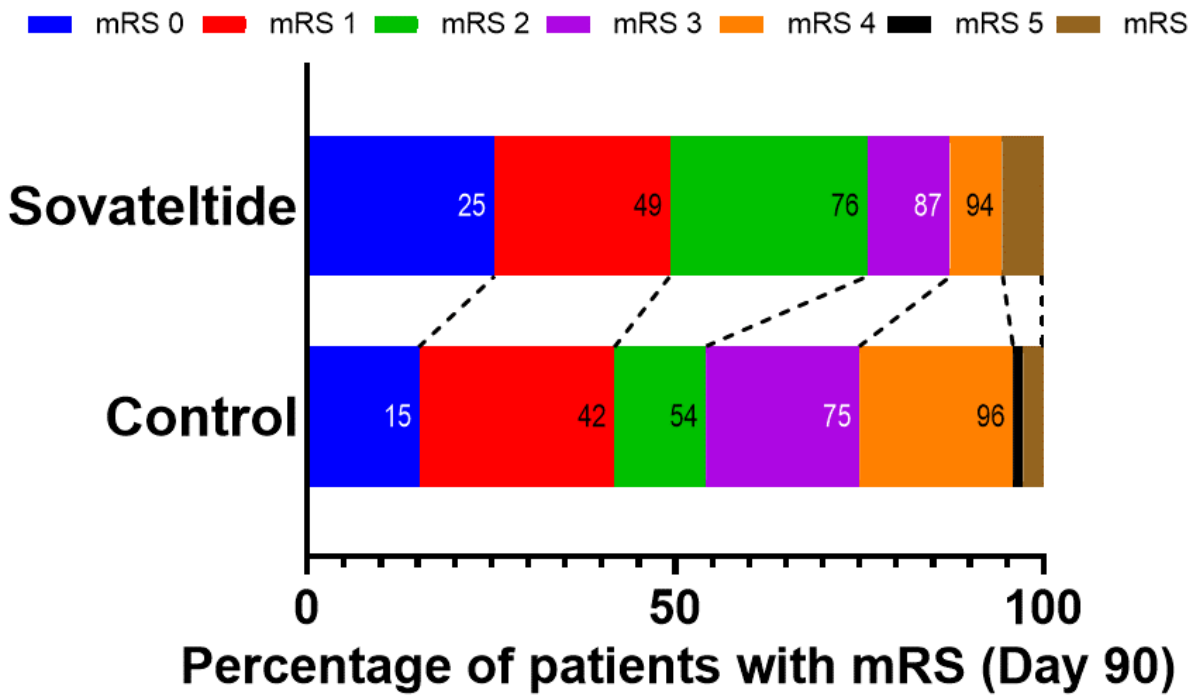
Summary of Trial Outcomes (Sovateltide Meets Primary Endpoints)

Primary Outcomes	Control (N=70)	Sovateltide (N=67)	Treatment Effect	P Value
Modified Rankin scale at 90 days (Median Score (IQR))	2.00 (1.00 to 3.00)	1.00 (0.00 to 2.00)	Mean diff. = –0.622 95% CI –1.078 to –0.167	0.0078
NIHSS scale at 90 days (Median Score (IQR))	3.00 (0.00 to 6.00)	1.00 (0.00 to 3.00)	Mean diff. = –1.586 95% CI –2.600 to –0.573	0.0024
Barthel Index at 90 days (Median Score (IQR))	85.00 (60.0 to 100.0)	95.00 (80.0 to 100.0)	Mean diff. = 10.190 95% CI 2.375 to 18.000	0.0110
Improvement of ≥2 on Modified Rankin scale score at 90 days	52.86% (N=37)	76.12% (N=51)	Odds 2.843 95% CI 1.368 to 6.015	0.0045
Improvement of ≥6 points on the NIHSS at 90 days	64.29% (N=45)	82.09% (N=55)	Odds 2.546 95% CI 1.176 to 5.798	0.0190
Improvement of ≥40 points on the Barthel Index at 90 days	61.43% (N=43)	76.12% (N=51)	Odds 2.001 95% CI 0.938 to 4.276	0.0640

IQR=Interquartile range

Sovateltide

Ordinal shift across the range of modified Rankin scale at 90 days



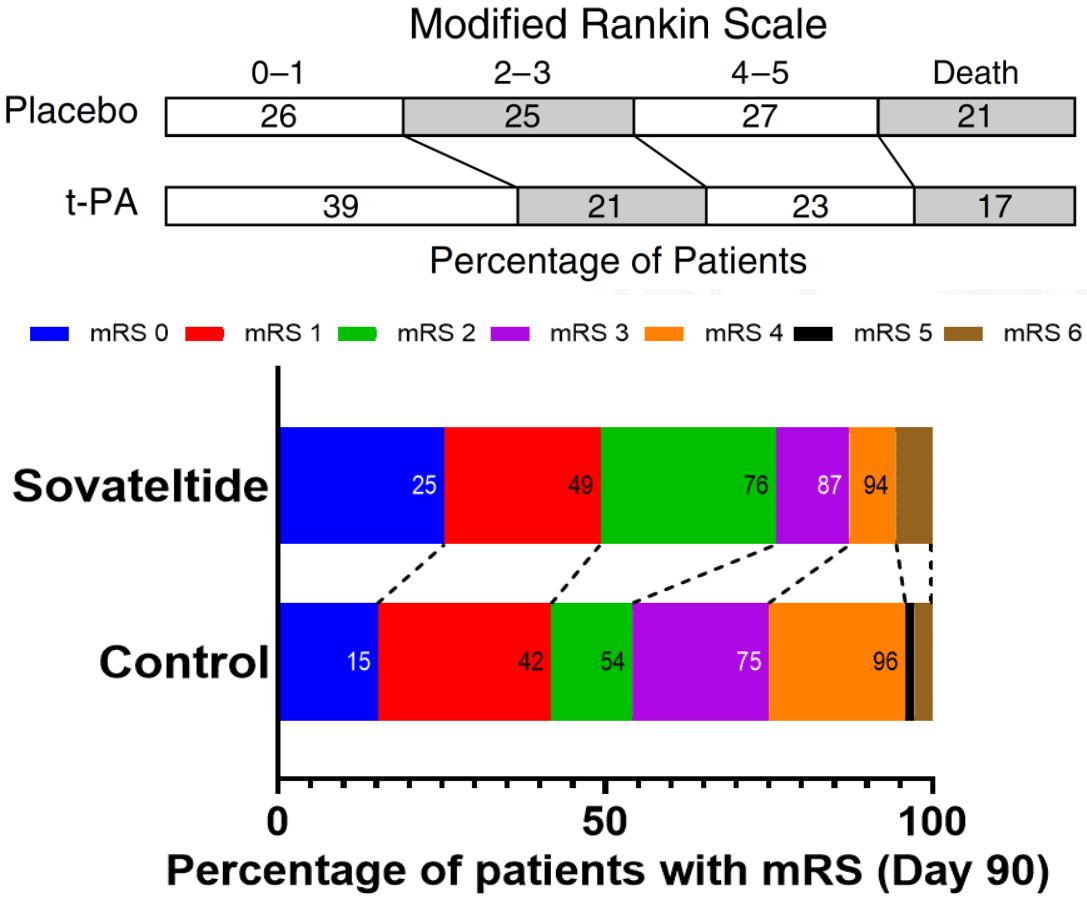
mRS	Control (N=72)	Sovateltide (N=71)
0	15.28% (N=11)	25.35% (N=18)
1	26.39% (N=19)	23.94% (N=17)
2	12.50% (N=9)	26.76% (N=19)
3	20.83% (N=15)	11.27% (N=8)
4	20.83% (N=15)	7.04% (N=5)
5	1.39% (N=1)	0.00% (N=0)
6	2.78% (N=2)	5.63% (N=4)

Distribution of scores on the Modified Rankin Scale at 90 days in the Intention-to-Treat population

The modified Rankin Scale (mRS) score is the most widely used primary outcome measure in trials for acute stroke interventions. A modified Rankin scale score of 0 indicates no disability, 1 no clinically significant disability, 2 slight disability, 3 moderate disability but able to walk unassisted, 4 moderately severe disability, 5 severe disability, and 6 death

Sovateltide: Additional Trial Results

Ordinal shift in mRS across the range at day 90 compared to the rt-PA stroke study



An absolute increase in favorable outcome of 9% was observed with t-PA in patients with mRS of 0 to 3

Sovateltide: Meets the key primary endpoint of mRS 0 to 2 at 90 days (p=0.002)

An absolute increase in favorable outcome of 12% was observed with Sovateltide in patients with mRS of 0 to 3

Number Needed to Treat (NNT) with Sovateltide is 5 compared to rt-PA of 10

Full recovery with Sovateltide in at least 10% more patients compared to standard treatment

Reference: The NINDS rt-PA Stroke Study Group, Tissue plasminogen activator for acute ischemic stroke, New England Journal of Medicine 1995, 333(24):1581-1587. Results of the present Phase III trial conducted in 158 patients of which 70 in patients in the control group and 67 patients in the sovateltide group completing the 90-day follow-up.

Sovateltide

A potential platform drug with multiple indications

- Tycamzzi augments neuronal progenitor cell differentiation and better mitochondrial morphology and biogenesis to activate a regenerative response in the central nervous system*
- Clinical trials demonstrate statistically significant and clinically meaningful improvement in neurological outcomes in patients with **acute cerebral ischemic stroke**.
- Tycamzzi is intended as a novel first-in-class therapeutic agent that is efficacious even when used within 24 hours of the onset of stroke symptoms
- Phase III trial demonstrates practice-changing results with a statistically significant and clinically meaningful improvement in neurological outcomes in acute cerebral ischemic stroke patients.

*Gulati et al., (2021) Safety and efficacy of sovateltide (IRL-1620) in a multicenter randomized controlled clinical trial in patients with acute cerebral ischemic stroke. CNS Drugs . 2021 Jan 11. doi: 10.1007/s40263-020-00783-9; PMID: 33428177; https://rdcu.be/cdps6

*Ranjan et al., Sci Rep. 2020 Jul 29;10(1):12737. doi: 10.1038/s41598-020-69673-w. PMID: 32728189

*Ranjan et al., Can J Physiol Pharmacol. 2020 Sep;98(9):659-666. doi: 10.1139/cjpp-2020-0164. PMID: 32574518

*Briyal et al., Sci Rep. 2019 Jul 18;9(1):10439. doi: 10.1038/s41598-019-46203-x. PMID: 31320660

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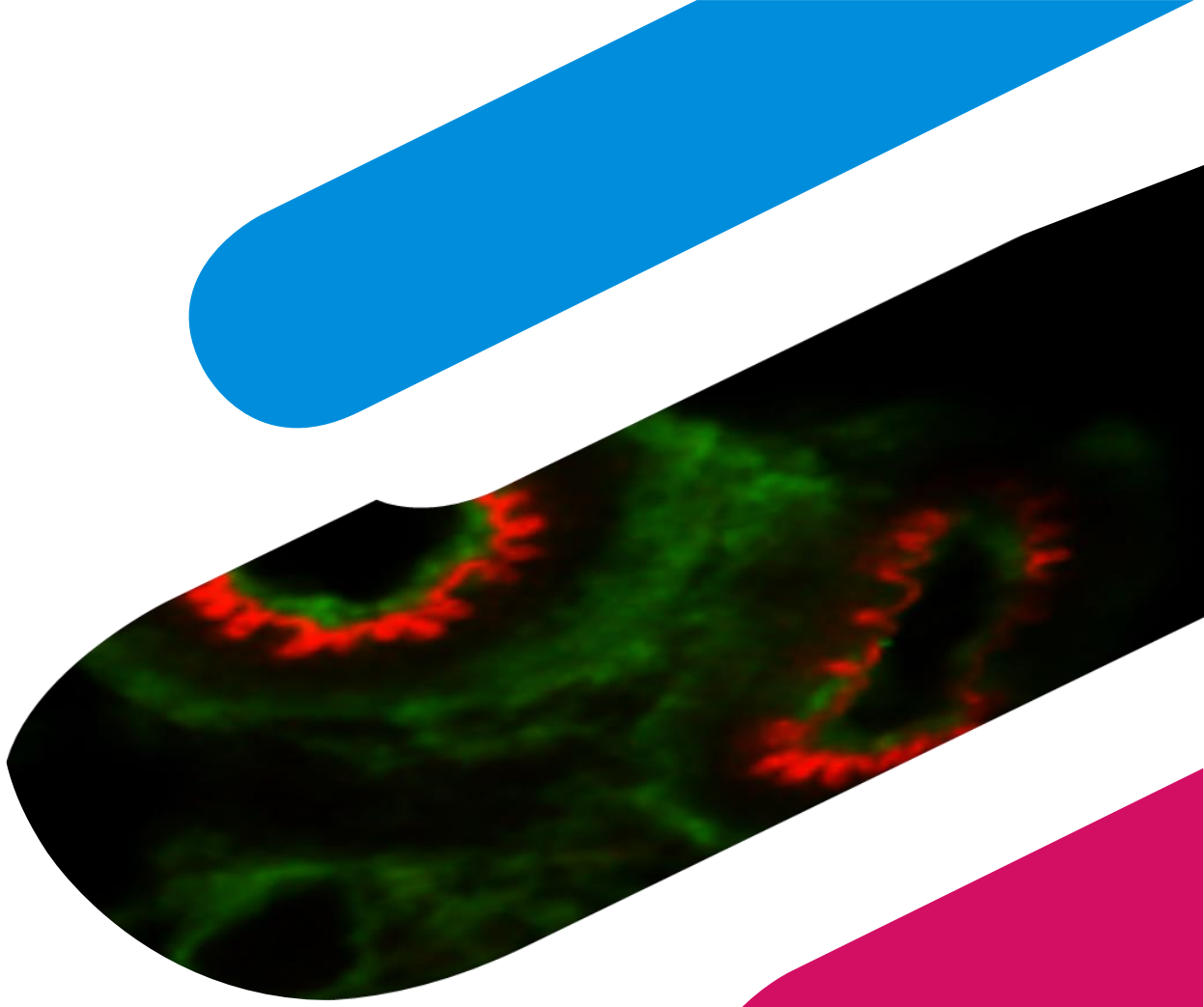

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