

THE LANCET Neurology

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: AFFINITY Trial Collaboration. Safety and efficacy of fluoxetine on functional outcome after acute stroke (AFFINITY): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2020; **19**: 651–60.

Supplementary Appendix

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Investigational Medicinal Product

Manufactured by Siegfried Malta Ltd (fluoxetine, certificate MT/008HM/2017) and Pharmaceutical packaging professionals (PPP) Pty Ltd (placebo)

Packaged by Amneal Pharmaceuticals Pty Ltd (Australian Therapeutic Goods Administration [TGA] licence holder).

Re-packaged (as patient kits, two bottles, each containing 110 capsules), labelled (with trial-specific treatment codes, fluoxetine or placebo), and distributed by PPP Pty Ltd.

Export to New Zealand and Vietnam approved by the Australian Government Department of Health TGA (Approval Ref No: EX17/336513).

Funding

National Health and Medical Research Council, Australia

Registration

Australian New Zealand Clinical Trial Registry number: ACTRN12611000774921

Sponsors

Royal Perth Hospital and Sir Charles Gairdner Hospital, Perth, Western Australia

Participating centres and number of patients randomised in each treatment group.

The participating centres are grouped by the highest to lowest recruiting country, followed by highest to lowest recruiting site. If centres have equal recruiting numbers, the sites are listed by alphabetical order. We have listed each centre by site number and name with the total number of patients recruited in [n], followed by names of the local principal investigator(s), and other significant contributors in that centre.

Vietnam [706 patients recruited]

Nguyen Tri Phuong Hospital [179] ((Tran Trung Thanh (PI), Le Tran Truc Mai Loan, Kieu Le Vu Thuy, Nguyen Van Sang, Nguyen Anh Diem Thuy, Dang Nhat Tam; Phan Thi Truc Hanh, Vo Thi Ngoc Loan, Nguyen Hue Mai, Dang Cao Hanh, Tran Thi Hong);

The Peoples Hospital 115 [110] (Nguyen Huy Thang (PI), Dam Thi Cam Linh, Ngo Thi Kim Trinh, Pham Nguyen Thanh Thai, Pham Nguyen Binh, Dao Thi Thanh Nha, Nguyen Thi Bich Huong, Le Thi Cam Linh, Do Minh Chi, Huynh Quoc Huy, Tran Thi Kim Giau, Le Thi Oanh, Tran Thi Khanh Ly)

Nghe An General Friendship Hospital [100] (Duong Dinh Chinh (PI), Kieu Van Duong, Le Na, Nguyen Ngoc Hoa, Le Van Binh, Nguyen Thanh Long, Nguyen Van Long, Dinh Quoc Tuan);

Gia Dinh Peoples Hospital [79] (Vo Van Tan (PI), Bui Ngoc Tram, Hoang Thi To Uyen, Nguyen Thi Bich Hien, Nguyen Thi Thu Ha, Lam Thuy Nga, Le Kim Khanh, Trinh Thanh Phuong, Huynh Quang Hop, Nguyen Thi Thu Thao, Lu Ngoc Huyen, Pham Hong Tham);

Thanh Hoa General Hospital [63] (Nguyen Hoanh Sam (PI), Le Hong Ninh, Nguyen Truong Giang, Doan Thi Bich, Pham Phuoc Sung, Luong Huu Duong, Mai Van Ha, Tran Van Thuc, Do Thi Phuong, Le Thi Hoai);

Bach Mai Hospital [61] (Nguyen Van Chi (PI), Nguyen Doan Phuong (PI), Mai Duy Ton, Dao Viet Phuong, Nguyen Tien Dung, Khuong Quoc Dai, Vuong Xuan Trung, Vu Tuong Lan, Ngo Duc Ngoc, Dang Hong Hanh, Truong Thai Phuong, Le Thi Ngan, Hoang Van Hoa, Do Quang Chung, Nguyen Thao Minh, Dam Hai Anh, Le Nhu Quynh);

Central Military Hospital 108 [42] (Nguyen Hoang Ngoc (PI), Nguyen Van Tuyen, Le Dinh Toan, Dinh Thi Hai Ha, Pham Van Cuong, Thach Thi Ngoc Khanh, Nguyen Hai Linh, Nguyen Thi Loan, Le Chi Vien, Tran Hong Phuong);

Cho Ray Hospital [33] (Nguyen Anh Tai (PI), Le Van Tuan, Truong Van Luyen, Bui Chau Tue, Huynh Xuan Ngoc, Dinh Van Lap, Pham Gia An, Le Thi Huyen Trang, Nguyen Tuong Vy, Nguyen Hai Yen);

University Medical Center [22] (Nguyen Ba Thang (PI), Thai Huy, Pham Thi Ngoc Quyen, Dao Duy Khoa, Pham Nguyen Bao Quoc, Dang Thi Huyen Thuong, Dinh Huynh To Huong, Tong Mai Trang, Vu Thi Thuy, Le Tri Si, Tran Ngoc Tai, Tran Hoai Phuong, Dinh Thuy Nhu Ngoc);

National Geriatric Hospital [17] (Nguyen Thanh Binh (PI), Do Phuong Vinh, Nguyen Ngoc Anh, Nguyen Thi Thanh Binh, Nguyen Thanh Binh).

Australia [532 patients recruited]

Sir Charles Gairdner Hospital, WA, [93] (David Blacker (PI), Graeme Hankey, Anne Claxton, Lindsey Bunce, Ai Ling Tan);

Fiona Stanley Hospital, WA, [80] (Darshan Ghia (PI), Gillian Edmonds, Nicole O'Loughlin, Megan Ewing, Kerri-Ann Whittaker, Lorrilee Deane);

Royal Perth Hospital, WA, [78] (Darshan Ghia (PI), Graeme Hankey, Anne Claxton);

Calvary Health Care Bruce, ACT, [34] (Yash Gawarikar (PI), Brett Jones, Maria Lopez, Koushik Nagesh, Emma Siracusa);

Royal Melbourne Hospital, VIC, [30] (Stephen Davis (PI), Amy McDonald, Jess Tsoleridis, Rachael McCoy, David Jackson, Gab Silver);

St John of God Hospital Midland, WA, [25] (Timothy R. Bates (PI), Amanda Boudville, Lynda Southwell);

Liverpool Hospital, NSW, [22] (Dennis Cordato (PI), Alan J McDougall, Cecilia Cappelen-Smith, Zeljka Calic, Shabeel Askar, Qi Cheng, Raymond Kumar);

Redcliffe Hospital, QLD, [18] (Richard Geraghty (PI), Maree Duroux, Megan Ratcliffe, Samantha Shone, Cassandra McLennan);

Ballarat Base Hospital, VIC, [16] (Ramesh Sahathevan (PI), Casey Hair);

Campbelltown & Camden Hospitals, NSW, [13] (Stanley Levy (PI), Beverley Macdonald, Benjamin Nham, Louise Rigney, Dev Nathani, Sumana Gopinath, Vishal Patel, Abul Mamun, Benjamin Trewin, Chun Phua, Ho Choong);

Belmont Hospital, NSW, [11] (Lauren Tarrant (PI) Kerry Boyle, Luisa Hewitt, Monique Hourn, Amanda Masterson, Kim Oakley, Karen Ruddell, Colette Sanctuary, Kimberley Veitch, Jenni White);

Blacktown Hospital, NSW, [11] (Richard Lindley (PI), Camelia Burdusel, Lina Lee, Gary Cheuk);

Shoalhaven District Memorial Hospital, NSW, [11] (Jeremy Christley (PI), Tabitha Hartwell, Craig Davenport, Kate Hickey, Rosanna Robertson, Michelle Carr);

Kingston Hospital, VIC, [10] (Peter New (PI) Sam Akbari, Hannah Coyle, Megan O'Neill, Cameron Redpath, Caroline Roberts, Marjan Tabesh, Toni Withiel);

Osborne Park Hospital, WA, [10] (Kapila Abeysuriya (PI), Andrew Granger (PI), Angela Abraham, Chermaine Chua, Dung Do Nguyen, Vathani Surendran, Melissa Daines, David Shivlal, Mudassar Latif, Noreen Mughal, Patricia Morgan);

Royal North Shore Hospital, NSW, [10] (Martin Krause (PI), Miriam Priglinger, Ehsan Esmaili Shandiz, Susan Day);

Swan District Hospital, WA, [9] (Timothy R. Bates (PI), Lay Kho);

Rankin Park Rehab Unit, NSW, [8] (Michael Pollack (PI) Judith Dunne, Helen Baines, Merridie Rees, Jenni White, Monique Hourn, Luisa Hewitt, Kimberley Veitch, Aicuratiya Withanage, Colette Sanctuary);

Royal Prince Alfred Hospital, NSW, [8] (Craig Anderson (PI), Candice Delcourt, Cheryl Carcel, Alejandra Malavera, Amy Kunchok, Elizabeth Ray);

Calvary Mater Newcastle, NSW, [6] (Elizabeth Pepper (PI) Emily Duckett, Jenni White, Kimberley Veitch, Luisa Hewitt, Monique Hourn, Kerry Boyle, Sally Ormond, Colette Sanctuary);

Lyell McEwin, SA, [6] (Andrew Moey (PI 2017-2019), Timothy Kleinig (PI 2016-2017), Vanessa Maxwell, Chantal Baldwin, Wilson Vallat, Deborah Field);

St Vincent's Hospital, NSW, [5] (Romesh Markus (PI), Kirsty Page, Danielle Wheelwright, Sam Bolitho, Steven Faux, Fix Sangvatanakul, Alexis Brown, Susan Walker, Jennifer Massey);

John Hunter Hospital, NSW, [4] (Michael Pollack (PI) (Jenni White (PI), Kimberley Veitch, Hillary Hayes, Luisa Hewitt, Monique Hourn, Colette Sanctuary);

Prince of Wales, NSW, [4] (Pesi Katrak (PI) (Annie Winker PI), Alessandro Zagami, Alanah Bailey, Sarah McCormack, Andrew Murray, Mark Rollason, Christopher Taylor);

Bankstown Hospital, NSW, [3] (Fintan O'Rourke PI), Ye Min Kuang, Heike Burnet, Yvonne Liu, Qi Cheng, Aileen Wu);

Caulfield Hospital, VIC, [2] (Peter New (PI), Sam Akbari, Hannah Coyle, Megan O'Neill, Diana Ramirez);

Footscray & The Sunshine Hospitals, VIC, [2] (Tissa Wijeratne (PI), Sherisse Celestino, Essie Low, Cynthia Chen, Jennifer Bergqvist);

Manly Hospital, NSW, [2] (Andrew Evans (PI) Queenie Leung);

Wagga Wagga Base Hospital, NSW, [1] (Martin Jude (PI), Rachael McQueen, Katherine Mohr, Latitia Kernaghan);

Flinders Medical Centre, SA, (Andrew Lee (PI), Paul Stockle, Boon Loong Tan, Sara Laubscher);

Participating Australian State and Territory Abbreviation Key:

ACT = Australian Capital Territory

NSW = New South Wales

QLD = Queensland

SA = South Australia

VIC = Victoria

WA = Western Australia

New Zealand [42 patients recruited]

Hawke's Bay Hospital [14] (John Gommans (PI), Diana Schmid, Melissa Spooner);

Taranaki Base Hospital [14] (Bhavesh Lallu (PI), Bronwen Pepperell, John Chalissery);

Rotorua Hospital [8] (Karim Mahawish (PI), Susan DeCaigney, Paula Broughton, Karen Knight, Veronica Duque);

Wellington Hospital [6] (Harry McNaughton (PI), Jeremy Lanford, Vivian Fu, Lai-Kin Wong);

Supplementary table 1.**Methods of patient follow-up**

Method of Follow-up	Fluoxetine (n=642)	Placebo (n=638)	p-values (A,B)
Day 28			
Outpatient Clinic	345	356	
Telephone	195	212	
Hospital	76	57	
Other (e.g. email, home visit)	20	11	
Missing	2	1	
Total submitted	638	637	0.0928 (0.1290 ^B)
Day 90			
Outpatient Clinic	357	360	
Telephone	233	239	
Hospital	14	6	
Other (e.g. email, home visit)	21	26	
Missing	4	0	
Total submitted	629	631	0.2848 (0.1020 ^B)
Day 180			
Outpatient Clinic	295	321	
Telephone	300	287	
Other (e.g. email, home visit)	15	12	
Missing	2	1	
Total submitted	612	621	0.4410 (0.5879 ^B)

A. P-values are based on the combined methods of follow-up (in-hospital assessment, outpatient clinic, telephone, home visit, and email).

B. P-values in brackets include missing data as another category.

Supplementary table 2.

**Adherence to trial medication in each treatment group and overall:
temporary and permanent cessation at each follow-up**

	Fluoxetine (n=642), N (%)	Placebo (638), N (%)	Total (N= 1280), N (%)	p-value (chi-square test)
Temporary cessation				
0-1 month	46/638 (7.2)	37/637 (5.8)	83/1275 (6.5)	0.3104
1-3 month	34/629 (5.4)	28/631 (4.4)	62/1260 (4.9)	0.4270
3-6 month	19/612 (3.1)	14/621 (2.3)	33/1233 (2.7)	0.3551
Total*	87	71	158	
Permanent cessation				
0-1 month	44/633 (7.0)	46/635 (7.2)	90/1268 (7.1)	0.8390
1-3 month	34/624 (5.5)	30/629 (4.8)	64/1260 (5.2)	0.5850
3-6 month	27/612 (4.4)	24/621 (3.9)	51/1233 (4.1)	0.6296
Total	105	100	205	

* Some patients reported temporary cessation of trial drug on multiple occasions.

Supplementary table 3.

Compliance with trial medication (actual dosing history compared to the prescribed drug regimen of once daily, 7 times per week) in each treatment group and overall.*

Time point Average number of times medication taken weekly	Fluoxetine (n=642)	Placebo (638)	Total (N= 1280) N (%)	p-values
1 month				0.5703
0 times per week	26 /630 (4.1)	25 /631 (4.0)	51 /1261 (4.0)	
1-2 times per week	16 /630 (2.5)	9 /631 (1.4)	25 /1261 (2.0)	
3-4 times per week	8 /630 (1.3)	10 /631 (1.6)	18 /1261 (1.4)	
5-6 times per week	24 /630 (3.8)	17 /631 (2.7)	41 /1261 (3.3)	
7 times per week	556 /630 (88.3)	570 /631 (90.3)	1126 /1261 (89.3)	
Missing	8	6	14	
3 months				0.9398
0 times per week	63 /622 (10.1)	62 /625 (9.9)	125 /1247 (10.0)	
1-2 times per week	6 /622 (1.0)	6 /625 (1.0)	12 /1247 (1.0)	
3-4 times per week	7 /622 (1.1)	6 /625 (1.0)	13 /1247 (1.0)	
5-6 times per week	15 /622 (2.4)	10 /625 (1.6)	25 /1247 (2.0)	
7 times per week	531 /622 (85.4)	541 /625 (86.6)	1072 /1247 (86.0)	
Missing	7	6	13	
6 months				0.9190
0 times per week	72 /608 (11.8)	76 /616 (12.3)	148 /1224 (12.1)	
1-2 times per week	5 /608 (0.8)	5 /616 (0.8)	10 /1224 (0.8)	
3-4 times per week	6 /608 (1.0)	8 /616 (1.3)	14 /1224 (1.1)	
5-6 times per week	10 /608 (1.6)	15 /616 (2.4)	25 /1224 (2.0)	
7 times per week	515 /608 (84.7)	512 /616 (83.1)	1027 /1224 (83.9)	
Missing	4	5	9	

* Proportions were calculated based on non-missing observations.

Supplementary table 4.**Results from the ordinal and binary analyses of the mRS**

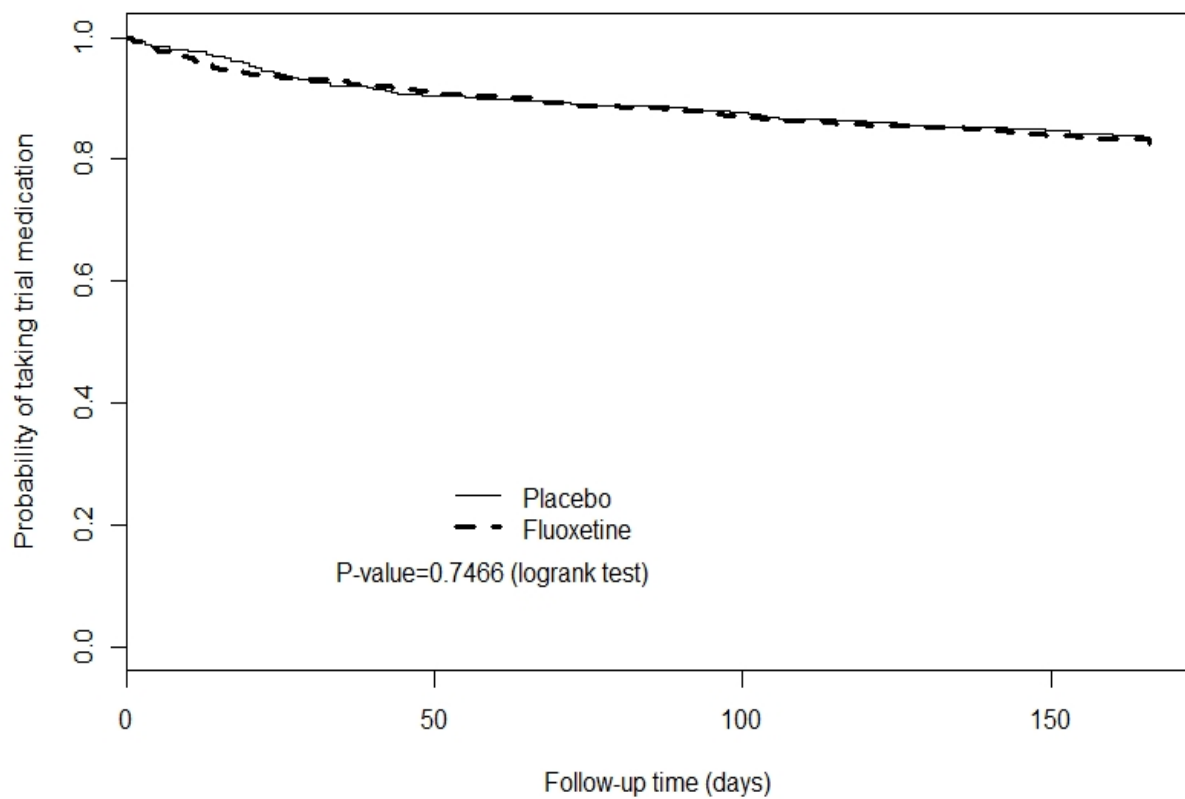
	Estimate (95%CI)	p-value
Unadjusted proportional odds model:		
Common odds ratio (OR)	0.97 (0.79 to 1.18)	0.7354
Adjusted proportional odds model*		
Common OR	0.94 (0.76 to 1.15)	0.5296
Unadjusted binary logistic regressions		
OR: 0 vs 1-6	0.95 (0.66 to 1.36)	0.7713
OR: 0-1 vs 2-6	1.02 (0.82 to 1.28)	0.8531
OR: 0-2 vs 3-6	0.86 (0.67 to 1.09)	0.2069
OR: 0-3 vs 4-6	1.04 (0.72 to 1.50)	0.8375
OR: 0-4 vs 5-6	0.99 (0.53 to 1.83)	0.9665
OR: 0-5 vs 6	0.99 (0.48 to 2.04)	0.9718

*The covariates used for the adjustment were the same as for the primary outcome analysis, that is, the analysis was adjusted for baseline minimization variables including delay since stroke onset computer-generated prediction of 6-month outcome, presence of a motor deficit and aphasia.

Supplementary table 5.**Sequential per-protocol analysis of the 1256 patients with mRS data at 6 months.**

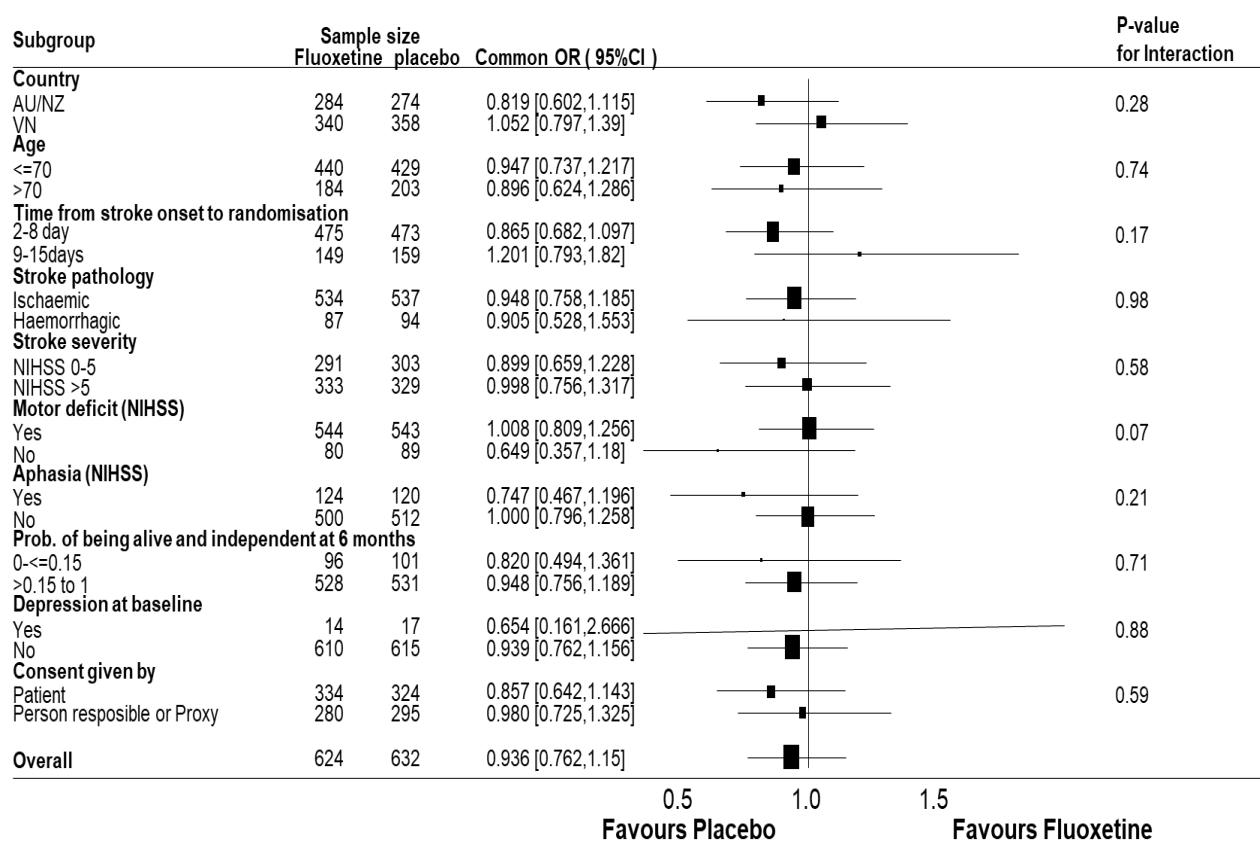
Groups cumulatively excluded	No. meeting each exclusion criteria	Cumulative no. removed from analysis	No. remaining in Fluoxetine group	No remaining in Placebo group	Common OR for mRS	95%CI	p-value	P-value (adjusted)
None –as per intention to treat analysis	0	0	624	632	0.97	0.79-1.18	0.7354	0.5296
1. Ineligible-didn't meet all inclusion criteria	4	4	621	631	0.97	0.79 -1.18	0.7354	0.5296
2. Received no trial medication	7	11	616	629	0.98	0.80 -1.20	0.8510	0.6361
3. Received <90 days of trial medication due to failure to follow trial procedures.	4	15	614	627	0.98	0.80 -1.20	0.8232	0.5413
4. Received <90 days of trial medication as chosen by patient, relative, or doctor, but not for adverse reactions.	30	45	598	613	0.97	0.79 -1.18	0.7412	0.4604
5. Received <90 days of trial medication due to suspected adverse reaction to the trial medication.	68	113	571	572	0.96	0.78 -1.17	0.6660	0.4068
6. Allocated to placebo but received an SSRI for > 10 days within the first 90 days	13	126	571	559	0.89	0.72 -1.10	0.2678	0.1309
7. Allocated to fluoxetine but received an SSRI for > 10 days within the first 90 days.	13	139	558	559	0.86	0.69 -1.06	0.1638	0.0783
8. Patients who did not complete at least 150 days of treatment	71	210	520	526	0.90	0.72 -1.11	0.3204	0.1600

This per-protocol analysis sequentially excluded subgroups of patients who either did not meet our eligibility criteria or had incomplete adherence to the trial medication, and shows the effect of fluoxetine vs placebo on the primary outcome of the mRS at 6 months for each subgroup.



Supplementary figure 1.

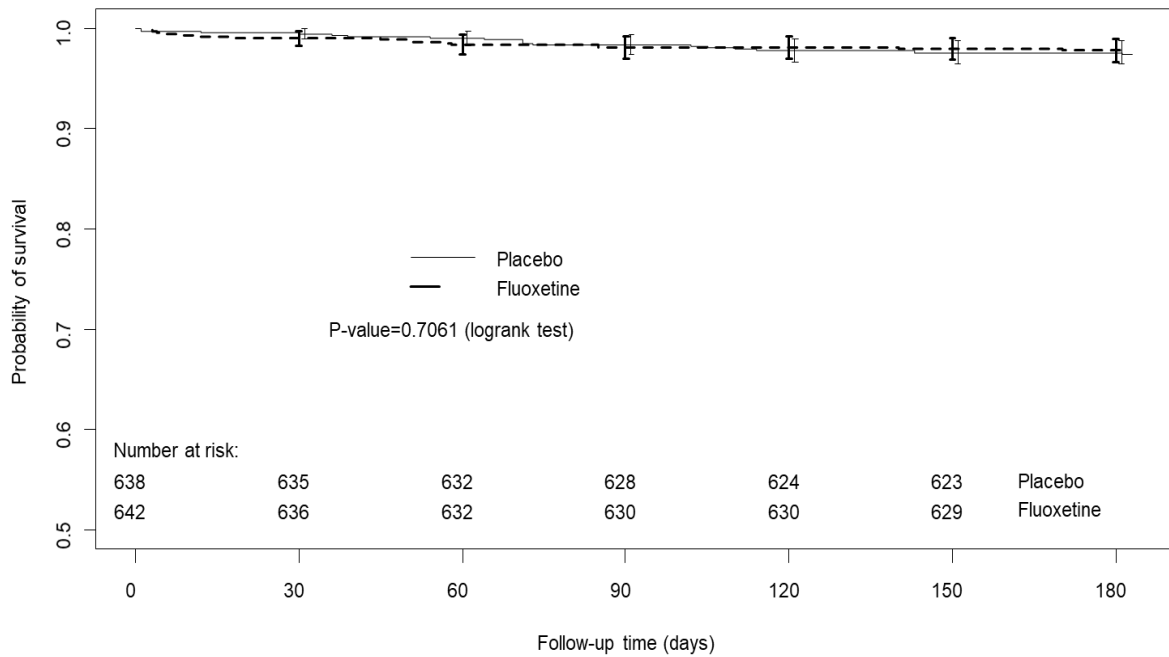
Kaplan Meier curve of time to permanent discontinuation of trial medication



Supplementary figure 2.

Primary outcome by pre-specified subgroups.

The primary efficacy outcome was shift in the modified Rankin scale score distribution (range 0 [no symptoms] to 6 [death]) at 6 months (180 days). For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events), and horizontal lines represent 95% CIs. Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits. Country: Country of randomization. AU/NZ: Australia, New Zealand. VN: Vietnam. NIHSS: National Institutes of Health Stroke Scale



Supplementary figure 3.

Kaplan Meier survival curve to 6 months follow-up.

Patients who withdrew consent to be followed-up were censored at the time of withdrawal from the trial.

Estimates, their 95% confidence intervals, and the number of patients at risk for each treatment group, are indicated for each time point after randomisation