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Twelve month outcomes of the AFFINITY trial of fluoxetine for functional recovery after acute stroke.

AFFINITY Trial Steering Committee on behalf of the AFFINITY trial Collaboration.

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Running title: Twelve month outcomes of the AFFINITY trial

Background and Purpose

The Assessment oF FluoxetINe In sTroke recoverY (AFFINITY) trial reported that oral fluoxetine 20 mg daily for 6 months after acute stroke did not improve functional outcome and increased the risk of falls, bone fractures, and seizures. After trial medication was ceased at 6 months, survivors were followed to 12 months post-randomization. This pre-planned secondary analysis aimed to determine any sustained or delayed effects of fluoxetine at 12 months post-randomization.

Methods

AFFINITY was a randomised, parallel-group, double-blind, placebo-controlled trial in adults (n=1280) with a clinical diagnosis of stroke in the previous 2-15 days and persisting neurological deficit who were recruited at 43 hospital stroke units in Australia (n=29), New Zealand (4), and Vietnam (10) between 2013 and 2019. Participants were randomised to oral fluoxetine 20mg once daily (n=642) or matching placebo (n=638) for 6 months and followed until 12 months after randomization. The primary outcome was function, measured by the modified Rankin scale (mRS), at 6 months. Secondary outcomes for these analyses included measures of the mRS, mood, cognition, overall health status, fatigue, health-related quality of life, and safety at 12 months.

Results

Adherence to trial medication was for a mean 167 (SD 48) days and similar between randomized groups. At 12 months, the distribution of mRS categories was similar in the fluoxetine and placebo groups (adjusted common odds ratio 0.93, 95% confidence interval 0.76-1.14; p=0.46). Compared to placebo, patients allocated fluoxetine had fewer recurrent ischemic strokes (14 [2.18%] vs 29 [4.55%]; p=0.02), and no longer had significantly more falls (27 [4.21%] vs 15 [2.35%]; p=0.08), bone fractures (23 [3.58%] vs 11 [1.72%]; p=0.05) or seizures (11 [1.71%] vs 8 [1.25%]; p=0.64) at 12 months.

Conclusions

Fluoxetine 20mg daily for 6 months after acute stroke had no delayed or sustained effect on functional outcome, falls, bone fractures, or seizures at 12 months post-stroke. The lower rate of recurrent ischemic stroke in the fluoxetine group is most likely a chance finding.

Key words

stroke, functional outcome, modified Rankin scale, fluoxetine, placebo, clinical trial

Clinical Trial Registration Information

Australian New Zealand Clinical Trial Registry http://www.anzctr.org.au;

number: ACTRN12611000774921

Non-standard Abbreviations and Acronyms

AFFINITY trial: Assessment oF FluoxetINe In sTroke recoverY trial

FLAME trial: FLuoxetine for motor recovery After acute ischeMic strokE trial

RCT: randomized controlled trial

SSRI: selective serotonin re-uptake inhibitor

mRS: modified Rankin scale

BDNF: brain-derived neurotrophic factor

GABA: gamma aminobutyric acid

IMP: investigational medicinal product

SIS: Stroke Impact Scale version 3

HRQOL: Health-related quality of life

PHQ-9: Patient Health Questionnaire 9

TICSm: Telephone Interview for Cognitive Status

Introduction

Stroke is a leading cause of lost disability-adjusted life years globally.[1] Fluoxetine, a selective serotonin re-uptake inhibitor (SSRI), was reported in 2011 to enhance upper and lower limb motor recovery, as measured with the Fugl-Meyer Motor Assessment Scale, after acute ischemic stroke in the FLuoxetine for motor recovery After acute ischeMic strokE (FLAME) trial.[2] Proposed mechanisms included increased expression of brain-derived neurotrophic factor (BDNF), reduced extracellular concentrations of gamma aminobutyric acid (GABA), and augmented activity-dependent plasticity in the brain.[3]

A subsequent Cochrane systematic review of 52 randomised controlled trials (RCTs) of SSRIs for stroke recovery in 4059 patients concluded that SSRIs may improve disability but, given methodological limitations and heterogeneity of the studies, more definitive trials were required.[4]

The Assessment oF FluoxetINe In sTroke recoverY (AFFINITY) recently reported that among 1280 patients with acute (2-15 days) stroke, oral fluoxetine, 20 mg daily for 6 months after acute stroke, did not improve functional outcome at 6 months compared to placebo, and increased the risk of falls, bone fractures, and epileptic seizures.[5] The results were consistent with those of two other large trials undertaken concurrently with similar designs.[6,7]

As stated in the trial protocol and statistical analysis plan,[8,9] the AFFINITY trial continued to follow surviving participants for a further 6 months after stopping trial medication, to examine whether any effects of fluoxetine during the first 6 months, were sustained or delayed at 12 months after randomization.

Methods

The anonymised data that support the findings of this trial are available to other researchers from the corresponding author (GJH) following receipt of a written request and proposal for

use of the data, approval by the AFFINITY trial Steering Committee, and establishment of a data sharing agreement.

The design, methods and primary results of the AFFINITY trial have been published.[5,8,9] Briefly, AFFINITY was a randomised, double-blind, placebo-controlled clinical trial conducted in 43 hospital stroke units in Australia (n=29), New Zealand (4), and Vietnam (10). All participating sites received approval from their ethics committee and institutional review board.

Eligible patients were adults (aged ≥18 years) with a clinical diagnosis of acute stroke within the previous 2-15 days, brain imaging consistent with ischemic or hemorrhagic stroke, and a persisting neurological deficit that produced a mRS score ≥1. Patients were excluded if there was a definite indication for fluoxetine, or contraindication to fluoxetine; if patients were unlikely to be available for follow-up during the subsequent 12 months; if patients had another life-threatening illness that would make 12-month survival unlikely; if women were pregnant, breast-feeding or of child-bearing age and not using contraception; or if patients were enrolled in another clinical trial of an investigational medicinal product (IMP) or device.

Written informed consent was obtained from each patient or, if the patients were unable to provide consent, from their legally approved surrogate.

Randomisation was via a secure, password-protected, centralised, web-based system which used a minimisation algorithm[10] and assigned patients to fluoxetine or placebo in a 1:1 ratio. Placebo capsules were visually identical to the fluoxetine capsules even when broken open. Fluoxetine 20mg capsules or matching placebo capsules were administered orally, once daily, for 6 months. All patients received organised, interdisciplinary care and rehabilitation in stroke units.

Patients recruited in Australia and New Zealand were followed-up at 180 days (6 months) and 365 days (12 months) by postal questionnaire or telephone, by trained staff in the trial coordinating center in Perth, Australia. Patients recruited in Vietnam were assessed by the site investigator at 180 days (6 months) and 365 days (12 months) post-randomization in the

hospital ward or outpatient clinic, or via telephone or email; or, failing that, at the patient's residence. If the patient was unable to complete the assessments, assistance was sought from their proxy (next of kin, close family member or carer). At the 12-month assessment, the mRS (table 1), other secondary outcomes including mood, cognition, overall health status (Stroke Impact Scale), fatigue and health-related quality of life (HRQoL, table 2), safety outcomes (table 3), and all current medications, were recorded. If the patient answered "yes" to any secondary outcome or safety outcome, investigators were asked to complete an outcome event form immediately to verify the diagnosis. Patients and outcome assessors remained masked to the allocated trial treatment at the 12-month assessment.

Outcomes

The primary outcome of the trial was functional status, as measured by the mRS,[11] at 6 months after randomization, as previously reported.[5]

Secondary outcomes at 12 months (which are the subject of this report), were the mRS,[11] mood (PHQ-9 score[12]), cognition (Telephone Interview for Cognitive Status [TICSm][13]), communication, motor function, overall health status (Stroke Impact Scale [SIS] version 3.0[14]), fatigue (vitality subscale of the SF-36[15,16]), and HRQoL using the EuroQoL EQ-5D-5L.[17]

Safety outcomes during follow-up included death, recurrent stroke (ischemic or hemorrhagic), acute coronary syndromes, upper gastrointestinal bleeding requiring blood transfusion and/or endoscopy, other major bleeding (subdural, extradural, ocular, lower gastrointestinal) requiring blood transfusion or procedural intervention, epileptic seizures, falls with injury, new bone fractures, new hyponatremia (blood sodium < 125mmol/L), symptomatic hypoglycemia (blood glucose < 3mmol/L), new depression (PHQ-9 score > 15[12]), and attempted or actual suicide or self-harm.

Statistical analysis

The statistical analysis plan published before recruitment was completed and without awareness of any unblinded data.[9]

The mRS scores at 12 months in each treatment group were analyzed using ordinal logistic regression before and after adjusting for the baseline factors included in the minimization

algorithm.[5,9] A post-hoc analysis also adjusted for all the baseline covariates listed in appendix table 2. The result was expressed as a common odds ratio (OR less than 1.0 favored placebo) and its 95% confidence interval (CI).

The frequencies of the categorical secondary outcome events in each group were compared using Fisher's exact test. For continuous secondary outcomes, the mean or median in each group, depending on the distribution, were calculated with measures of dispersion (standard deviation [SD] or inter-quartile range [IQR]). The probability that outcomes in the fluoxetine group were significantly different from the placebo group were calculated as p-values.

All analyses were by intention-to-treat, according to the treatment allocation, among patients for whom outcome data were available, and undertaken with SAS, version 9.4. A post-hoc per protocol analysis of the mRS at 12 months in each treatment group was also undertaken which excluded participants who didn't start the allocated trial medication, permanently stopped taking the allocated trial medication, or reported taking open label fluoxetine or another SSRI.

The trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12611000774921.

Results

A total of 1280 patients consented and were randomised at 43 sites in Australia, New Zealand and Vietnam between January 11, 2013 and June 30, 2019. Recruitment was terminated before the target of 1600 patients was reached because funding expired on December 31, 2019.

642 patients were randomly allocated to fluoxetine and 638 to placebo (fig 1). The baseline characteristics in the two groups were balanced (Supplementary table I).[5]

The mean duration of trial treatment was 167 days (SD 48.1) days. There was no significant difference between groups in adherence to trial medication.[5]

By 12 months, 26 (2.0%) survivors had withdrawn consent for follow-up, 3 (0.2%) were lost to follow-up, and 1 (0.1%) was followed up at 12 months but the mRS was not recorded.

At the end of the trial treatment period at 6 months after randomization, 42 (3.2%) patients reported that they were taking open label fluoxetine or another SSRI (18 had been randomised to fluoxetine, and 24 to placebo). At 12 months after randomization, 64 (5%) patients were taking open label fluoxetine or another SSRI (32 had been randomised to fluoxetine, and 32 placebo); 29 of these patients had continued to take open label SSRI since the 6 month follow-up (14 randomized to fluoxetine, and 15 placebo), and 35 of these patients had started taking open label SSRI after ceasing study drug at 6 months (18 randomised to fluoxetine, and 17 placebo).

The mRS at 12 months was assessed and analysed in 620 (96.6%) patients allocated fluoxetine and 630 (98.7%) placebo. The distribution of ordinal data from the mRS at 12 months, adjusted for variables in the minimization algorithm, was similar in both groups (common OR 0.93, 95% CI 0.76-1.14; p=0.46; table 1). The unadjusted analysis produced similar results (common OR 0.93, 95%CI 0.76-1.14; p=0.50; table 1). A post-hoc analysis that adjusted for all the baseline covariates listed in appendix table 2, also revealed no significant effect of fluoxetine vs placebo on the mRS at 12 months. A post-hoc per protocol analysis also produced similar results (adjusted OR: 0.88, 95% CI: 0.70-1.10, p=0.25; common OR: 0.87, 95%CI: 0.70-1.09, p=0.24; supplementary table II).

There was no significant difference between treatment groups in any of the other secondary efficacy outcomes at 12 months (table 2).

Table 3 shows that there was also no significant difference between treatment groups in any of the safety outcomes at 12 months, with the exception of a lower incidence of ischemic stroke at 12 months among patients allocated 6 months treatment with fluoxetine compared to placebo (14 [2.18%] vs 29 [4.55%]; p=0.02). At 12 months there was no longer a significant difference in falls (27 [4.21%] vs 15 [2.35%]; p=0.08), bone fractures (23 [3.58%] vs 11 [1.72%]; p=0.054) and epileptic seizures (11 [1.71%] vs 8 [1.25%]; p=0.64) which had been observed at 6 months.[5]

Discussion

In this ethnically diverse clinical trial population, fluoxetine 20mg daily for 6 months after acute stroke had no effect on functional outcome at 6 or 12 months. Although exposure to trial fluoxetine for 6 months was associated with increased rates of falls, bone fractures, and

seizures, this difference was no longer statistically significant at 12 months. The only difference between the fluoxetine and placebo groups at this longer time point was a reduction in recurrent ischemic stroke in patients allocated fluoxetine compared to placebo.

These results indicate that routine treatment with fluoxetine for 6 months after acute stroke increased the risk of seizures, falls, and fractures but had no effect on functional outcome at 6 months. After fluoxetine was ceased, the lack of effect on functional outcome persisted and the excess risk of falls, seizures and fractures attenuated.

The mechanisms by which fluoxetine temporarily increased the risk of falls, seizures and fractures within the first 6 months are uncertain but may include orthostatic hypotension[18], increased lower limb spasticity perhaps[19], somnolence[20], sleep disorders[20], heart rhythm disorders[20]; and lowering bone mineral density.[21-23]

It is unclear why the functional outcome of participants was not affected by the increased risk of seizures, falls and fractures at 6 months in the fluoxetine group. One possibility is that the excess proportion of patients who experienced these adverse effects of fluoxetine was too small to impact the overall distribution of the mRS. Another possibility is that participants who experienced adverse effects of fluoxetine had recovered by the time they were assessed by the mRS. A further possibility is that the mRS is insensitive to mild changes in functional capacity of stroke survivors.

Our finding of a lower rate of ischemic stroke at 12 months among patients allocated fluoxetine compared to placebo is probably a chance finding due to random error associated with analyses of numerous secondary outcome measures. Although the result is consistent with a lower 3-year rate of recurrent ischemic stroke reported in another randomized trial of fluoxetine versus placebo, given for 3 months after acute ischemic stroke in a total of 404 patients[24], a lower rate of ischemic stroke at 6 months was not observed among larger populations of acute stroke patients allocated fluoxetine in the FOCUS[6] and EFFECTS[7] trials. The FOCUS trial has also reported no difference in functional outcome or secondary efficacy outcomes at 12 months after exposure to fluoxetine daily in the first 6 months after stroke, but rates of safety outcomes and ischemic stroke at 12 months have not been reported.[25] More reliable estimates of any

effects of fluoxetine will be forthcoming in a planned meta-analysis of the individual patient data from the FOCUS, EFFECTS and AFFINITY trials.

Conclusions

Fluoxetine 20 mg daily for 6 months after stroke did not improve functional outcome at 6 or 12 months after randomisation but did increase the incidence of bone fractures, falls and seizures during the 6 month period of treatment with fluoxetine, which attenuated over the 6 months after fluoxetine was ceased. The lower rate of recurrent ischemic stroke at 12 months after randomization in the fluoxetine group is most likely a chance finding.

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Table 1.

Modified Rankin Scale (mRS) score at 12 months after randomisation

(6 months after cessation of trial medication)

Modified Rankin Scale (mRS)		Fluoxetine (n=642) N (%)	Placebo (n=638) N (%)
0	No symptoms	89 (14.4)	104 (16.5)
1	No clinically significant disability despite symptoms	267 (43.1)	258 (41.0)
2	Slightly disability: unable to do everything	90 (14.5)	104 (16.5)
3	Moderately disability: unable to live independently but can walk	106 (17.1)	97 (15.4)
4	Moderately disability and unable to walk without help from another person	33 (5.3)	39 (6.2)
5	Severe disability: unable to sit up	8 (1.3)	7 (1.1)
6	Dead	27 (4.4)	21 (3.3)
Total		**620**	**630**

Ordinal proportional odds model:

Common odds ratio: 0.93, 95%CI: 0.76-1.14, p=0.50

Adjusted odds ratio: 0.93, 95% CI: 0.76-1.14, p=0.46

Covariates adjusted for:

- Delay between and stroke and randomisation (days)
- Probability of being alive and independent at 6 months
- Motor deficit
- Aphasia

Table 2.

Secondary outcomes at 12 months after randomization by allocated treatment group

	Fluoxetine (n=642)			Placebo (n=638)			
	N*	**Median**	**IQR**	**N***	**Median**	**IQR**	**P value****
Mood (PHQ-9)	525	2.0	(0.0-4.0)	516	2.0	(0.0-4.0)	0.64
Cognition (TICSm)	514	24.0	(20.0-28.0)	521	24.0	(20.0-28.0)	0.22
Stroke Impact Scale (SIS) domains							
Strength	554	75.0	(62.5-100.0)	574	75.0	(62.5-100.0)	0.33
Memory/Thinking	554	92.9	(78.6-100.0)	574	92.9	(75.0-100.0)	0.68
Emotions	554	83.3	(69.4-91.7)	574	80.6	(66.7-88.9)	0.053
Communication	553	100.0	(92.9-100.0)	574	100.0	(89.3-100.0)	0.26
Daily Activities	554	92.5	(72.5-100.0)	574	90.0	(72.5-100.0)	0.67
Mobility	553	91.7	(69.4-100.0)	574	88.9	(69.4-100.0)	0.24
Hand ability	553	90.0	(60.0-100.0)	574	90.0	(65.0-100.0)	0.43
Participation	553	84.4	(62.5-100.0)	574	84.4	(62.5-100.0)	0.92
Recovery (VAS)	533	80.0	(70.0-90.0)	557	80.0	(70.0-90.0)	0.65
Motor†	554	85.9	(65.7-97.4)	574	84.4	(65.7-95.8)	0.31
Physical function‡	554	87.5	(67.6-97.4)	574	86.0	(66.8-96.3)	0.35
Vitality (SF-36)	540	75.0	(60.0-85.0)	557	70.0	(60.0-80.0)	0.48
EQ-5D-5L	545	0.85	(0.66-1.0)	562	0.84	(0.63-1.0)	0.39

* The number of patients with each of the secondary outcome scores. Data were only available for those who survived and who completed sufficient questions to derive a score.

**Mann-Whitney test

PHQ-9: Patient Health Questionnaire 9 items (higher score indicates more depressive symptoms)

TICSm: Telephone Interview for Cognitive Status (higher scores are better)

SIS: Stroke Impact Scale (where higher scores are better).

†Mean of the Strength, Hand ability, and Mobility domains.

‡Mean of the Strength, Hand ability, Mobility, and Daily activities domains.

VAS: visual analogue scale.

SF-36: 36 item short form questionnaire (higher scores indicate less fatigue, more energy)

EQ-5D-5L: EuroQoL - 5 Dimensions (Mobility, Personal Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) - 5 Levels (where 1 indicates the best health imaginable, and 0 indicates the worst health imaginable).

Table 3. Safety outcomes at 12 months after randomization by allocated treatment.

	Fluoxetine (n=642)		Placebo (n=638)				
	n	%	n	%	Difference %	95% CI (%)	P-value (Fisher exact)
Death	27	4.21	21	3.29	0.91	-1.17 to 2.99	0.46
Any stroke	25	3.89	36	5.64	-1.75	-4.08 to 0.58	0.15
All thrombotic events							
Ischemic stroke	14	2.18	29	4.55	-2.36	-4.34 to -0.39	0.02
Acute coronary events	3	0.47	3	0.47	-0.00	-0.75 to 0.75	1.00
All bleeding events							
Hemorrhagic stroke	6	0.93	2	0.31	0.62	-0.24 to 1.48	0.29
Upper GI bleed	2	0.31	2	0.31	-0.00	-0.61 to 0.61	1.00
Epileptic seizures	11	1.71	8	1.25	0.46	-0.86 to 1.78	0.65
Fall with injury	27	4.21	15	2.35	1.85	-0.09 to 3.80	0.08
New bone fracture	23	3.58	11	1.72	1.86	0.10 to 3.62	0.054
Hyponatremia < 125mmol/L	4	0.62	2	0.31	0.31	-0.44 to 1.06	0.69
Symptomatic hypoglycemia	1	0.16	0	0	0.16	-0.15 to 0.46	1.00
New depression	51	7.94	57	8.93	-0.99	-4.04 to 2.06	0.55
New antidepressant	51	7.94	55	8.62	-0.68	-3.70 to 2.34	0.69
Attempted or actual suicide	0	0	2	0.31	-0.31	-0.75 to 0.12	0.25
Other safety outcome	92	14.3	98	15.36	-1.03	-4.93 to 2.87	0.64

GI: gastrointestinal

Footnote:

Only adjudicated events were counted and each event was counted once for each patient.

New depression and new antidepressant were accumulated from all follow-up forms (28, 90, 180 and 365 days).

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Profs Almeida, Flicker, Ford, Billot, Jan, Lundström, Sunnerhagen, Thang-Nguyen, Gommans, and Yi report no conflicts.

Supplemental Materials

Online Supplementary Tables I, II

APPENDIX

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Uyen-Ha	Hong
Linh-Thi My	Le
Tram-Thi Bich	Ngo
Yen-Bao	Mai
Huyen-Thanh	Han
Nhu-Quynh	Truong
Huong-Thi	Nguyen
Hai-Thanh	Ngo
-Thi Binh	Nguyen
Oanh-Thi Kieu	Ha
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Peter	New
Andrew	Lee
Thanh-Trung	Tran

Loan-Tran Truc Mai	Le
Thuy-Le Vu	Kieu
Sang-Van	Nguyen
Thuy-Anh Diem	Nguyen
Tam-Nhat	Dang
Hanh-Thi Truc	Phan
Loan-Thi Ngoc	Vo
Mai-Hue	Nguyen
Hanh-Cao	Dang
Hong-Thi	Tran
Linh-Thi Cam	Dam
Trinh-Thi Kim	Ngo
Thai-Nguyen Thanh	Pham
Binh-Nguyen	Pham
Nha-Thi Thanh	Dao
Huong-Thi Bich	Nguyen
Linh-Thi Cam	Le
Chi-Minh	Do
Huy-Quoc	Huynh
Giau-Thi Kim	Tran
Oanh-Thi	Le
Ly-Thi Khanh	Tran
Chinh-Dinh	Duong
Duong-Van	Kieu
Na	Le
Hoa-Ngoc	Nguyen
Binh-Van	Le
Long-Thanh	Nguyen
Long-Van	Nguyen
Tuan-Quoc	Dinh
Tan-Van	Vo
Tram-Ngoc	Bui
Uyen-Thi To	Hoang
Hien-Thi Bich	Nguyen
Ha-Thi Thu	Nguyen
Nga-Thuy	Lam
Khanh-Kim	Le
Phuong-Thanh	Trinh
Hop-Quang	Huynh
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Tham-Hong	Pham
Sam-Hoanh	Nguyen
Ninh-Hong	Le
Giang-Truong	Nguyen
Bich-Thi	Doan
Sung-Phuoc	Pham
Duong-Huu	Luong
Ha-Van	Mai

Thuc-Van	Tran
Phuong-Thi	Do
Hoai-Thi	Le
Chi-Van	Nguyen
Phuong-Doan	Nguyen
Ton-Duy	Mai
Phuong-Viet	Dao
Dung-Tien	Nguyen
Dai-Quoc	Khuong
Trung-Xuan	Vuong
Lan-Tuong	Vu
Ngoc-Duc	Ngo
Hanh-Hong	Dang
Phuong-Thai	Truong
Ngan-Thi	Le
Hoa-Van	Hoang
Chung-Quang	Do
Minh-Thao	Nguyen
Anh-Hai	Dam
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Ngoc-Hoang	Nguyen
Tuyen-Van	Nguyen
Toan-Dinh	Le
Ha-Thi Hai	Dinh
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Khanh-Thi Ngoc	Thach
Linh-Hai	Nguyen
Loan-Thi	Nguyen
Vien-Chi	Le
Phuong-Hong	Tran
Tai-Anh	Nguyen
Tuan-Van	Le
Luyen-Van	Truong
Tue-Chau	Bui
Ngoc-Xuan	Huynh
Lap-Van	Dinh
An-Gia	Pham
Trang-Thi Huyen	Le
Vy-Tuong	Nguyen
Yen-Hai	Nguyen
Thang-Ba	Nguyen
Huy	Thai
Quyen-Thi Ngoc	Pham
Khoa-Duy	Dao
Quoc-Nguyen Bao	Pham
Thuong-Thi Huyen	Dang
Huong-Huynh To	Dinh
Trang-Mai	Tong
Thuy-Thi	Vu

Si-Tri	Le
Tai-Ngoc	Tran
Phuong-Hoai	Tran
Ngoc-Thuy Nhu	Dinh
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Vinh-Phuong	Do
Anh-Ngoc	Nguyen
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Abul	Mamun
Benjamin	Trewin
Chun	Phua
Ho	Choong
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Kerry	Boyle
Luisa	Hewitt
Monique	Hourn
Amanda	Masterson
Kim	Oakley
Karen	Ruddell
Colette	Sanctuary
Kimberley	Veitch
Camelia	Burdusel
Lina	Lee
Gary	Cheuk
Jeremy	Christley
Tabitha	Hartwell
Craig	Davenport
Kate	Hickey
Rosanna	Robertson
Michelle	Carr
Sam	Akbari
Hannah	Coyle
Megan	O'Neill
Cameron	Redpath
Caroline	Roberts
Marjan	Tabesh
Toni	Withiel
Kapila	Abeysuriya
Andrew	Granger
Angela	Abraham
Chermaine	Chua
Dung	Do Nguyen
Vathani	Surendran
Melissa	Daines
David	Shivlal
Mudassar	Latif
Noreen	Mughal
Patricia	Morgan
Martin	Krause
Miriam	Priglinger
Ehsan E.	Shandiz
Susan	Day
Lay	Kho

Michael	Pollack
Judith	Dunne
Helen	Baines
Merridie	Rees
Jenni	White
Monique	Hourn
Kimberley	Veitch
Aicuratiya	Withanage
Colette	Sanctuary
Candice	Delcourt
Cheryl	Carcel
Alejandra	Malavera
Amy	Kunchok
Elizabeth	Ray
Elizabeth	Pepper
Emily	Duckett
Jenni	White
Kimberley	Veitch
Luisa	Hewitt
Monique	Hourn
Kerry	Boyle
Sally	Ormond
Colette	Sanctuary
Andrew	Moey
Timothy	Kleinig
Vanessa	Maxwell
Chantal	Baldwin
Wilson	Vallat
Deborah	Field
Romesh	Markus
Kirsty	Page
Danielle	Wheelwright
Sam	Bolitho
Steven	Faux
Fix	Sangvatanakul
Alexis	Brown
Susan	Walker
Jennifer	Massey
Michael	Pollack
Jenni	White
Kimberley	Veitch
Hillary	Hayes
Luisa	Hewitt
Monique	Hourn
Colette	Sanctuary
Pesi	Katrak
Annie	Winker
Alessandro	Zagami
Alanah	Bailey

Sarah	Mccormack
Andrew	Murray
Mark	Rollason
Christopher	Taylor
Fintan	O'Rourke
Ye Min	Kuang
Heike	Burnet
Yvonne	Liu
Qi	Cheng
Aileen	Wu
Sam	Akbari
Hannah	Coyle
Megan	O'Neill
Diana	Ramirez
Tissa	Wijeratne
Sherisse	Celestino
Essie	Low
Cynthia	Chen
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Andrew	Evans
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Latitia	Kernaghan
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Diana	Schmid
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Bhavesh	Lallu
Bronwen	Pepperell
John	Chalissery
Karim	Mahawish
Susan	DeCaigney
Paula	Broughton
Karen	Knight
Veronica	Duque
Harry	McNaughton
Jeremy	Lanford
Vivian	Fu
Lai-Kin	Wong

Figure 1: AFFINITY trial profile mRS=modified Rankin Scale

*No. of patients who did not submit form (due to death or withdrawal of consent) between days 180 and 365.