AMOBES (Active Mobility Very Early After Stroke)
A Randomized Controlled Trial
Alain P. Yelnik, MD; Victorine Quintaine, MD; Cedric Andriantsifanitra, MD; Marie Wannepain, PT; Peggy Reiner, MD; Hélène Marnef, PT; Mathilde Evrard, PT; Elena Meseguer, MD; Jean Pascal Devailly, MD; Monica Lozano, PT; Catherine Lamy, MD; Florence Colle, MD; Eric Vicaut, MD, PhD; on behalf of the AMOBES Group*

Background and Purpose—Intensive physical therapy (PT) facilitates motor recovery when provided during a subacute stage after stroke. The efficiency of very early intensive PT has been less investigated. We aimed to investigate whether intensive PT conducted within the first 2 weeks could aid recovery of motor control.

Methods—This multicentre randomized controlled trial compared soft PT (20 min/d apart from respiratory needs) and intensive PT (idem+45 minutes of intensive exercises/day) initiated within the first 72 hours after a first hemispheric stroke. The primary outcome was change in motor control between day (D) 90 and D0 assessed by the Fugl–Meyer score. Main secondary outcomes were number of days to walking 10 m unassisted, balance, autonomy, quality of life, and unexpected medical events. All analyses were by intent to treat.

Results—we could analyze data for 103 of the 104 included patients (51 control and 52 experimental group; 64 males; median age overall 67 [interquartile range 59–77], 67 right hemispheric lesions, 80 ischemic lesions, National Institutes of Health Stroke Scale score ≥8 for 82%). Fugl–Meyer score increased over time (P<0.0001), with no significant effect of treatment (P=0.29) or interaction between treatment and time (P=0.40). The median change in score between D90 and D0 was 27.5 (12–40) and 22.0 (12–56) for control and experimental groups (P=0.69). Similar results were found for the secondary criteria.

Conclusions—Very early after stroke, intensive exercises may not be efficient in improving motor control. This conclusion may apply to mainly severe stroke.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01520636.

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Key Words: acute stroke ■ exercise therapy ■ physical therapy ■ rehabilitation ■ stroke

In the early stage after stroke, within the first 2 weeks, physical therapy (PT) has 2 main goals: prevent immobility-related events and stimulate motor control recovery. However, the amount of PT to provide and the time after stroke for provision remain unclear.

The organization of care in multidisciplinary stroke units has reduced the risk of death and dependency after stroke, with early mobilization and rehabilitation having an important role. Very early mobilization (VEM) was defined by the AVERT group (A Very Early Rehabilitation Trial): within the first 24 hours, focusing on out-of-bed activity (sitting, standing, walking), provided at least 3× more than usual care, by physical therapists or nurses. VEM has been found safe and feasible, with a significant positive effect on recovery of walking 50 m unassisted, good functional prognosis on Barthel index at 3 months, and for the frequency of severe complications. Hemorrhagic stroke patients showed a better level of function (walking >15.24 m). The recent European recommendations and those from the American Stroke Association promote VEM, although how early and how much a patient should be mobilized remains controversial. Some negative impact of early (<24 hours) versus delayed (<48 hours) physical rehabilitation has been reported, with increased risk of death.
After the question of the time for exercise is the question of the amount. Regarding VEM, the later publication by the AVERT group\textsuperscript{11} definitely found that too much early mobilization is detrimental for prognosis. VEM is beneficial when provided 2 to 3 times per day, and this number should not be increased.

The other and main goal for PT after stroke is to stimulate motor and sensory recovery. This goal needs specific intensive training directed to deficiencies, different from mobilization, which is a global approach of activity. Such physical rehabilitation has been found more effective for neural plasticity when provided at the subacute stage after stroke. Most studies took place within the first 3 months, beginning after 10 to 15 days at the earliest after stroke.\textsuperscript{12} The role of early intensive training is still unknown. The early period seems crucial for neural plasticity stimulation, as observed in animals\textsuperscript{13,14} and humans.\textsuperscript{15,16} However, animal models showed that intensive exercises given too early may worsen the cerebral ischemia.\textsuperscript{17,18} Finally, in reviewing 47 studies in animals, Austin et al\textsuperscript{19} suggested that early-initiated (24–48 hours postsstroke), moderated, forced exercises, 10 m/min, 5 to 7 days/week for ≈30 minutes can be recommended.

Few studies of humans investigated the role of intensive PT within the first 15 days after stroke. A positive impact on walking was observed, but intensive training consisted of only 20 minutes/d.\textsuperscript{20} No beneficial effect of intensive training was observed in another study,\textsuperscript{21} or the benefit was limited to patients with mild stroke.\textsuperscript{22} The VECTORS trial (Very Early Constraint-Induced Movement During Stroke Rehabilitation) showed a negative effect of high-intensity constraint-induced movement therapy (90% of walking hours) and rehabilitation (3 hours/d).\textsuperscript{23}

We aimed to compare active and intensive PT conducted within the first 2 weeks after stroke and conservative soft PT in improving recovery of motor control and independence.

Methods

### Study Design

This was a prospective randomized open-labelled trial with blinded endpoint (PROBE) conducted in 9 French stroke units with physical and rehabilitation medicine (PRM) teams (see Appendix 1, the AMOBES Group, and the online-only Data Supplement for the number of inclusion per center).

Because the 2 treatments were different, knowledge of the hypothesis and the different treatments would have affected patients’ behavior. To avoid this possible bias, the study was conducted according to a Zelen design,\textsuperscript{24} whereby patients did not know PT for the other group.

The software CleanWeb, developed by Telemedicine Technology S.A, was used for centralized randomization. Stratification was by stroke unit, age ≤75/>75 years, and stroke severity according to the National Institutes of Health Stroke Scale (NIHSS) (score ≤8/8–15/>15).

PT according to the protocol began once the patient was randomized, within the first 72 hours, and ended after 2 weeks (ie, 10 sessions) or at stroke unit discharge. Blinded assessment was ensured as follows: assessments were conducted by an evaluator physical therapist different from the treating physical therapist, in a PRM department, not in the stroke unit, for motor control, walking, and balance and by a blinded PRM physician for unexpected events, length of stay, independence, and quality of life.

All data were monitored from clinical files as sources documents by clinical research assistants of the Clinical Research Unit (Lariboisière-St-Louis).

To minimize differences, each center was involved in the trial’s conception, and all staffs at the sites were trained for both the intervention and assessments by the main investigator and the physical therapists of the investigator’s center.

The study was promoted by Assistance Publique-Hôpitaux de Paris, approved by the local ethics committee (no. 2011/37), and registered at ClinicalTrials.gov (NCT01520636).

### Participants

Inclusion criteria were age ≥18 years, first unilateral hemispheric stroke, ischemic or hemorrhagic stroke, upper- or lower-limb motor deficiency assessed by at least a score ≥2 for the sixth item of the NIHSS at inclusion, signed informed consent, and social health insurance. We included patients with persistent deficiencies between 25 and 72 hours after a stroke. Exclusion criteria were conscious disorders (score ≥2 for the first item of the NIHSS), complete recovery within the first 24 hours, brain stem or cerebellar stroke, previous history of neurological disorder, severe language disorder preventing from understanding the protocol, brain surgery for the current stroke, modified Rankin score other than 0 before stroke, and surgery scheduled within the next 15 days. All participants gave their written consent before inclusion.

### Procedure

#### Interventions

The control group received soft PT, to prevent immobility-related events, 15 to 20 minutes/d apart from respiratory needs at least 5 days a week. The physical therapist had to accompany the patient without anticipating ability: passive limb mobilization, sitting posture when allowed, help with walking if possible. Besides the physical therapist intervention, the nursing staff and relatives assisted with the patient’s mobilization (setting up in a bed or chair, ambulation) according to the medical prescription and the usual rules of the stroke unit. This time of mobilization was not monitored. Self-rehabilitation was not encouraged.

The experimental group received intensive PT defined as the same treatment as the control group but with 45 minutes of intensive exercises per day. Active intensive PT was customized and applied to the limbs and the trunk with the patient in and out of bed according to their capacity. PT involved repetition of movements, resistance applied, length of each exercise, oral stimulation adapted to the patient’s performance and always at the upper limit of their capacity. For example, flexion and extension of the elbow, present, were trained repetitively until the sensation of fatigue, against an adapted resistance by the therapist. Sitting, standing, and walking had to be systematically trained, except in case of medical contraindication, with internal or external constraints customized by the therapist. All techniques were allowed for these trainings.

### Outcomes

The patient characteristics recorded were sex, age, NIHSS score at the time of inclusion, stroke type (ischemic or hemorrhagic), stroke side and site, and thrombolysis if conducted.

The primary outcome was the change in motor control between D90 and D0 assessed by the motor domain of the Fugl–Meyer score, removing the item related to reflexes as proposed by Lindmark.\textsuperscript{25} Secondary outcomes were the number of days to walking 10 m without human assistance; balance assessed by the Postural Assessment Scale for Stroke at D30 and D90; autonomy assessed by the modified Rankin scale at D15, D30, D45, D90 and by the motor subscore of the Functional Independence Measurement at D30 and D90; quality of life assessed by the Stroke Impact Scale at D90; total unexpected medical events; total length of stay in the stroke and PRM units; and where the patient was living at D90.

### Statistical Analysis

Analyses were based on intent to treat. Continuous variables with normal distribution are expressed as mean±SD and with non-Gaussian distribution as median (interquartile range; tested by Shapiro–Wilk method) and qualitative variables as number (%). The possible effect of treatment on the time-dependent changes in Fugl–Meyer score.
between D0 and D90 (ie, primary outcome) were analyzed by non-parametric analysis of variance because of non-Gaussian distribution of the variable. We also introduced in the analysis of variance model several factors a priori known to potentially affect outcome (NIHSS at the time of inclusion; stroke type, side, and site; thrombolysis) to test whether they affected treatment. In addition, absolute changes in Fugl–Meyer score between D90 and D0 were compared by Mann–Whitney test. Similar analyses were made for Postural Assessment Scale for Stroke, Functional Independence Measurement, and Stroke Impact Scale measurements. In addition, sensitivity analyses were made replacing missing values for patients who died by the worse possible value of the studied score. Number of days to walking 10 m without human assistance and total length of stay in the stroke and PRM units were compared by competitive risk (ie, death) analyses and Gray’s test after stratification by NIHSS score at the time of inclusion. Changes from baseline in modified Rankin scale were compared by χ² test. Complications occurring between D0 and D90 and where the patient was living at D90 were analyzed after stratification by NIHSS score with Mantel Haenzel statistics and Breslow–Day test for homogeneity of odds ratios. All tests involved used SAS 9.4 or R software. P<0.05 was considered statistically significant.

Sample Size Calculation
Considering a standard deviation of 15 for the Fugl–Meyer score and an intrapatient correlation of values around 0.8, and 15% attrition, we calculated that we needed 200 patients per group for analysis of variance comparison with 80% power to detect a treatment effect and 90% power to detect an interaction time×treatment effect with a difference in Fugl–Meyer score of 8 between the 2 groups at D90.

Results
From July 4, 2012, to December 2, 2014, we included 104 patients (Figure 1 and Table 1). Data for 103 patients could be analyzed, for 51 in the control group and 52 in the experimental group. Characteristics did not differ between the groups. Most patients (n=97, 94%) had a previous medical history: 72 with high blood pressure (35 controls versus 37 experimental); 20 with diabetes mellitus (9 versus 11); 8 with cardiac infarction (2 versus 6), 3 because of respiratory insufficiencies (2 versus 1); 2 with cardiac insufficiencies (1 versus 1), and 75 with other diseases or disorders (36 versus 39) but none of the excluded pathologies.

Primary Outcome
Analysis of time-dependent changes in Fugl–Meyer score demonstrated a significant increase in score over time (Figure 2; P<0.0001) but no significant effect of treatment (P=0.29) or interaction of treatment and time (P=0.40). Similar conclusions were found on introducing in the analysis NIHSS score at the time of inclusion; type, side, and site of the stroke; and thrombolysis and when replacing missing values for patients who died by the worse possible value of the studied score. Control and experimental groups did not differ in change in score (P=0.69; Table 2). A sensitivity analysis of patients not meeting inclusion criteria led to the same conclusions.

Figure 1. Flow chart of trial.
Table 1. Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th></th>
<th>Control Group n=51</th>
<th>Experimental Group n=52</th>
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<tbody>
<tr>
<td>Sex, M/F</td>
<td>29/22</td>
<td>35/17</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>65.0 (58.0–78.0)</td>
<td>67.0 (61.0–75.5)</td>
</tr>
<tr>
<td>Time (hours) between stroke and randomization, median (IQR)</td>
<td>53.0 (32.0–69.0)</td>
<td>55.5 (42.0–67.5)</td>
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Stroke

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<tr>
<th></th>
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<tbody>
<tr>
<td>Side right/left</td>
<td>35/16</td>
<td>32/20</td>
</tr>
<tr>
<td>Ischemic/hemorrhagic</td>
<td>41/10</td>
<td>39/13</td>
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Site of ischemic lesion

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>MCA superficial</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>Deep</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>ACA</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>PCA</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>MCA+ACA</td>
<td>4</td>
<td>1</td>
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Thrombolysis

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<thead>
<tr>
<th></th>
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<th>Experimental Group</th>
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<tbody>
<tr>
<td>NIHSS &lt;8</td>
<td>9 (8.7%)</td>
<td>10 (9.7%)</td>
</tr>
<tr>
<td>8–15</td>
<td>21 (20.4%)</td>
<td>21 (20.4%)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>21 (20.4%)</td>
<td>21 (20.4%)</td>
</tr>
<tr>
<td>Fugl–Meyer (min 0–max 98), median (IQR)</td>
<td>7 (1–18)</td>
<td>9.5 (2.0–28.5)</td>
</tr>
</tbody>
</table>

Data are no. or no. (%) of patients unless indicated. ACA indicates anterior cerebral artery; IQR, interquartile range; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; and PCA, posterior cerebral artery.

Secondary Outcomes

Analysis of time-dependent changes in Postural Assessment Scale for Stroke between D0 and D90 demonstrated a significant increase in score with time (P<0.0001), but no significant effect of treatment (P=0.85) or interaction between treatment and time (P=0.93; Table 2). Median delay to achieve walking among the whole population did not differ between the control and experimental groups: 41 (interquartile range 25.0–93) and 42.5 (23.5–87) days (P=0.95).

The modified Rankin scale was 0 to 2 for 9 patients (4 control and 5 experimental group) at D30 and for 29 (14/15) at D90. The 2 groups did not differ in changes from baseline in modified Rankin scale (P>0.4 at all times) or Functional Independence Measurement (P=0.55).

The total number of unexpected medical events at D90 was 231. The number of involved patients was the same in each group: 36 control and 39 experimental group. Some differences, although not significant, appeared depending on the type of event: 47 falls in 22 patients (7 versus 15), 17 chest infections in 16 patients (10 versus 6), 11 cardiac events in 10 patients (4 versus 6), 9 neurological vascular events in 9 patients (4 versus 5), 5 epilepsy events in 4 patients (4 versus 0), and 2 deep venous thrombosis with one pulmonary embolism (0 versus 2).

The 2 groups did not differ in quality of life as measured by the 8 questions of the Stroke Impact Scale (P>0.55 for all items) or median visual analogic scale at D90: 65 (interquartile range 50–90) versus 70 (interquartile range 50–75; P=0.99).

At D90, 6 patients (5.8%) had died (2 control and 4 experimental group); only 33 had returned home (13 versus 19) or entered an institution (0 versus 1). The other 58 were still inpatients in a PRM department (6 missing data).

Discussion

Our randomized controlled trial is the first to test intensive PT very early after stroke, for all patients beginning within the first 3 days, but failed to show a positive impact on motor recovery.

The main limitation of this study is the relatively low number of patients. The estimated required population size was 400 participants, calculated on the basis of the known evolution of motor control measured with the Fugl–Meyer scale, to observe an 8-point difference between groups. Unfortunately, patient inclusion was difficult, so we stopped the study in December 2014, 29 months after opening the first center. Nevertheless, the current study enrolled among the highest number of patients for this kind of trial in humans. Moreover, on the basis of these real data, a new calculation has been made to estimate the required population to observe a possible difference between groups: the size of the population should be at least 4000 participants. Therefore, the expectation to observe a positive effect of intensive PT early after stroke with this study design is small and the feasibility of such a study is low. Thus, despite our small sample, results make sense.

Another limitation is because of some deviations to the protocol criteria: 11 patients were included a few hours after the 72nd hour, one with a brain stem stroke and one with a previous silent stroke. Because the analyses were based on intent to treat, all patients were considered in the analyses. Unfortunately, the number of the total screened patients could not be monitored.

The last limitation, but also interesting, is that our population does not reflect the whole population of stroke units. Our sample is characterized by patients with severe stroke, very low motor control, relatively young age, active treatment (40% benefitted from thrombolysis), and relatively low occurrence of death. So, although the lack of difference is consistent in each severity subgroup because the mild subgroup was small, our results could suggest that intensive PT is not needed early, especially after moderate and severe stroke. Whether the intensity of PT should be adapted to the severity of stroke deserves further investigation because other studies also observed negative results among patients with severe but also with mild or moderate stroke, with NIHSS score ranging from 4 to 12.

Then the question addressed by this trial is the usefulness of intensive active PT in the acute stage after stroke. To stimulate recovery by means of neural plasticity, intensity of rehabilitation was found effective, but most of the studies were conducted with patients at the subacute stage, from 2 weeks to 3 months. Very few studies have been conducted on intensive early training in humans, and drawing conclusions from animal studies is difficult because of many differences between animal models and humans.

Intensity is a relative concept. The type of exercise differs among studies, the constant being more than in the control...
group. This type can be considered too vague but in our opinion is the best way to differentiate PT between groups. In our study, to easily adapt the exercise to each patient, we defined intensity by longer time (45 minutes/d more than in the control group), repetition of movements, and difficulty applied at the limit of the patient’s performance. In an open study with positive results, patients were provided 20 minutes/d of intensive walking training, by human or robotic assistance, added to 55 minutes of gait-oriented PT. This can be considered moderately intensive exercise. Conversely, the negative results from the VECTOR trial resulted from a really high intensity of constraint-induced movement therapy (90% walking hours) and rehabilitation (3 hours/d) as compared with 6 hours of constraint-induced movement therapy and 2 hours/d of rehabilitation. In another randomized controlled trial, the 2 groups received really early intensive rehabilitation (3 hours/d, 6 days/week) because the objective was to compare constraint-induced movement therapy to traditional therapy. No difference was observed. The study by Di Lauro et al found no difference between relatively intensive exercises, 2 hours/d of treatment, including 45 minutes of active work, versus 45 minutes of ordinary rehabilitative treatment. In the EXPLICIT randomized controlled trial (Explaining Plasticity After Stroke), patients with severe stroke received 2 sessions of 30 minutes of an electromyography-triggered neuromuscular stimulation of the finger extensors, without positive effect.

Finally, our results agree with those from previous studies, which allows for drawing recommendations for rehabilitation early after stroke. We suggest distinguishing among goals for early rehabilitation, prevention of immobility-related events, and stimulation of motor recovery, even if there is some overlap among them. To prevent immobility-related events, VEM has been found efficient. Provided from the 24 or 48 hours, the best amount seems to be 2 to 3 times per day. To stimulate motor control recovery, fundamental studies give arguments for early initiation of training, but we have no evidence to recommend intensive training within the first days. The severity of the stroke probably should be taken into account. One of the issues is to know whether early neural plasticity is not in a good phase or whether training can have any impact because of the severity of the deficiencies and general status of the patient.

To conclude, very early after stroke, especially after moderate or severe stroke, intensive exercises directed on the deficiencies may not be more effective on motor recovery than a

<table>
<thead>
<tr>
<th>Table 2. Results of Testing</th>
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<tbody>
<tr>
<td>Score (Min–Max)</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Fugl–Meyer (0–88)</td>
</tr>
<tr>
<td>Control</td>
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<tr>
<td>Experimental</td>
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<tr>
<td>Change D90–D0</td>
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<tr>
<td>Control</td>
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<tr>
<td>Experimental</td>
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<tr>
<td>PASS (0–36)</td>
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<td>Control</td>
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<td>Experimental</td>
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<tr>
<td>mRS (0–6)</td>
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<tr>
<td>Control</td>
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<tr>
<td>Experimental</td>
</tr>
<tr>
<td>FIM (18–91)</td>
</tr>
<tr>
<td>Control</td>
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<tr>
<td>Experimental</td>
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<tr>
<td>Walk 10 m, no. (%)</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Experimental</td>
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</table>

Data are median (interquartile range) unless indicated. FIM indicates Functional Independence Measurement; mRS, modified Rankin score; and PASS, Postural Assessment Scale for Stroke.
soft global PT preventing immobility-related complications, which remains mandatory.

Appendix AMOBES Group

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Disclosures

None.

References


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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/12/22/STROKEAHA.116.014803.DC1

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Active Mobility very Early after Stroke (AMOBES): a randomized controlled trial

SUPPLEMENTAL MATERIAL

Electronic appendix: Number of inclusions per center

Paris Lariboisière University Hospital: 15
Paris Bichat University Hospital: 28
Paris Pitié-Salpétrière University Hospital: 14
Paris St Anne University Hospital: 23
Paris St Joseph University Hospital: 8
Brest University Hospital: 4
Créteil Henri Mondor University Hospital: 3
Grenoble University Hospital: 6
Nancy University Hospital: 3