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1 **Real-world assessment of LCI following lumacaftor-ivacaftor initiation in adolescents and adults**  
2 **with cystic fibrosis**

3  
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40 **Abstract**

41 Lung clearance index (LCI) is a biomarker of ventilation inhomogeneity. Data are scarce on its  
42 usefulness in daily practice for monitoring the effects of treatments in older children and adults with  
43 CF. In this French observational study of lumacaftor-ivacaftor, 63 of 845 patients (7.5%) had available  
44 LCI performed at baseline and at six (M6; n=34) or 12 months (M12; n=46) after lumacaftor-ivacaftor  
45 initiation. At inclusion, median [IQR] age was 16 years [13-17], ppFEV<sub>1</sub> was 72.8 [59.6-80.7], and LCI  
46 was 12.3 [10.3-15.0]. At both M6 and M12, no statistically significant LCI increases of 0.13 units or  
47 1.34% (95% CI: -4.85-7.53) and 0.6 units or 6.66% (95% CI: -0.03-13.5) were observed. Discordant  
48 results between LCI and ppFEV<sub>1</sub> were observed in one-third of the patients. In daily practice, LCI  
49 monitoring in adolescents and young adults with moderate lung disease gives results that are more  
50 heterogenous than those reported in children with milder disease.

51

52 **Keywords:** lumacaftor, CFTR modulators, cystic fibrosis, multiple breath washout

53 **Running title:** LCI in real life

54

55 **Author's contribution.** **Philippe Reix** : conceptualization, data acquisition, test overreading, data  
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57 and editing; **Iulia Ioan:** data acquisition, writing review and editing, **Muriel Le bourgeois:** data  
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61 acquisition, writing review and editing, **Jennifer Da Silva:** data base management, writing review  
62 and editing, **Jean-Louis Paillasseur:** stastical analysis, writing review and editing, **Pierre Regis Burgel:**  
63 conceptualization, data acquisition, writing review and editing, visualization, project administration

64        **1. Introduction**

65        Multiple breath washout (MBW), which explores ventilation inhomogeneity, has been shown to be a  
66        valuable research tool (1). MBW-derived outcomes such as the lung clearance index (LCI) have been  
67        used as primary endpoints in phase 3 clinical trials to assess the effects of cystic fibrosis  
68        transmembrane conductance regulator (CFTR) modulators in young children who have cystic fibrosis  
69        (CF) but preserved lung function (2-4). An absolute decrease in the LCI, corresponding to a reduction  
70        in ventilation inhomogeneity, has consistently been reported throughout these trials. Recently, data  
71        from an observational cohort study (PROSPECT) conducted in a more diverse population of patients  
72        with CF who received follow-up in the year after lumacaftor-ivacaftor initiation have confirmed these  
73        findings (5).

74        Several pediatric CF centers in France have deemed it interesting to monitor this biomarker in the CF  
75        clinical setting. However, data obtained in clinical trials or in observational studies in experienced  
76        centers do not necessarily reflect those obtained in daily practice. In the present study, we took  
77        advantage of MBW measurements performed in a large national real-world observational study that  
78        followed CF patients aged 12 years or older over the first year after lumacaftor-ivacaftor initiation (6).  
79        Our goal was to describe LCI evolution following the initiation of lumacaftor-ivacaftor and to examine  
80        its clinical value as compared to ppFEV<sub>1</sub>. We hypothesized that LCI may provide clinically-relevant  
81        information that may be a useful complement to spirometry.

82        **2. Materials and methods**

83        **2.1 Patients**

84        The study design and organization of the French lumacaftor-ivacaftor observational cohort are  
85        described elsewhere (6, 7). That study was registered with (NCT03475391) and approved by the  
86        Institutional Review Board of The French Society for Respiratory Medicine (Société de Pneumologie  
87        de Langue Française, #2016–004). Patients and parents were informed of the protocol but were not

88 required to provide informed consent as per French law. Being observational by nature, there was no  
89 study power calculation.

## 90 **2.2 MBW measurements and outcomes**

91 All MBW measurements available from the participating CF centers were collected. Patients were  
92 considered eligible for this substudy if they had at least one MBW measurement performed at  
93 baseline (within 90 days prior to lumacaftor-ivacaftor initiation) and at least one measurement at six  
94 (M6) and/or 12 (M12) months after initiation. Six out of 11 pediatric CF centers with a MBW device  
95 participated in this sub-study. All were certified by the ECFS-CTN core facility, employed the same  
96 device (ExhalyzerD; Ecomedics, Duernten, Switzerland) for the nitrogen washout technique and had  
97 high levels of experience with this latter. MBW was performed either before or after a chest  
98 physiotherapy course, but always at the same timing throughout the study. MBWs were performed  
99 based on the ECFS standard operating procedure, and all traces were reviewed for quality  
100 assessment by a single investigator (PR).

101 Lung clearance indices were measured at the fortieth of initial nitrogen concentration (known as  
102  $LCI_{2.5}$  but referred to here as LCI) and used as the main MBW outcome.  $ppFEV_1$  was used as the main  
103 spirometry outcome. Absolute and relative changes were calculated.

## 104 **2.3 Statistics**

105 Data are presented as numbers and percentages (n, %), means with standard deviations (SD) and  
106 confidence intervals (95% CI), or medians with interquartile ranges (IQR) as pertinent. Data obtained  
107 for LCI or spirometry at initiation and at M6 and/or M12 were compared using the paired Wilcoxon's  
108 test. A  $P$  value  $<0.05$  was considered statistically significant. Pearson correlations were used between  
109 LCI and  $ppFEV_1$ . Concordant and discordant results between  $ppFEV_1$  and LCI were evaluated using  
110 cut-offs of relative changes of 10% and 15% respectively; the former being considered meaningful in  
111 clinical practice, the latter based on data published elsewhere (8-10).

112 **3. Results**

113 **3.1 Characteristics of patients**

114 At least one MBW was performed for 77 patients during the study. Six patients were excluded  
 115 because they had no LCI at initiation, or no LCI at either M6 or M12. Data from eight patients were  
 116 also excluded because their LCIs at initiation were not performed within the 90 days preceding  
 117 lumacaftor-ivacaftor administration. There was thus a final dataset of 63 patients including two  
 118 adults (Table 1). A total of 144 MBW measurements were collected from them.

119 **Table 1: Characteristics of the 63 CF patients at lumacaftor-ivacaftor initiation**

	Median [IQR]	Min-Max
Age (years)	16 [13-17]	12-20
BMI (Z-score)	-0.81 [-1.09-0.37]	-1.84-4.29
ppFEV <sub>1</sub>	72.8 [59.6-80.7]	33.0-101
ppFEV <sub>1</sub> <40	0 (0%)	
ppFEV <sub>1</sub> [40 to 90]	57 (90.5%)	
ppFEV <sub>1</sub> ≥90	6 (9.5%)	
LCI	12.3 [10.3-15.0]	6.8-23.3
ppFVC	86.5 [75.6-95.2]	50.2-128
Number of IV antibiotic courses* (n = 61)	0 [0-2]	0-4
PI n (%)	62 (98.4%)	
Diabetes	6 (9.6%)	
Liver cirrhosis	1 (1.6%)	

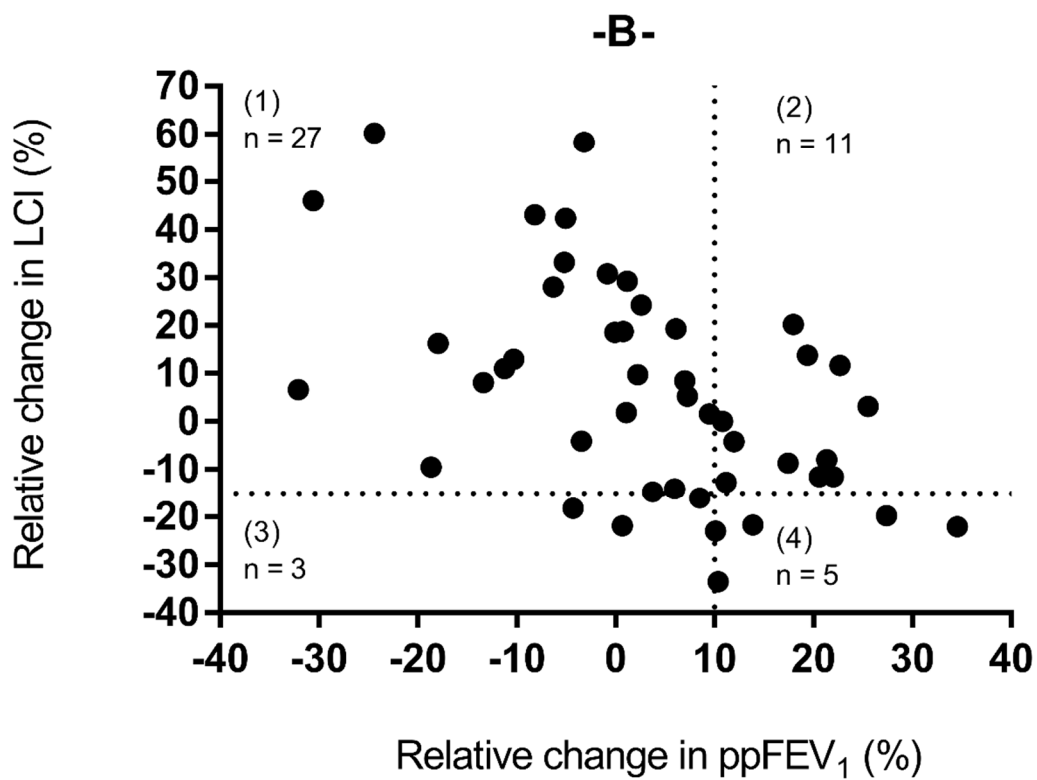
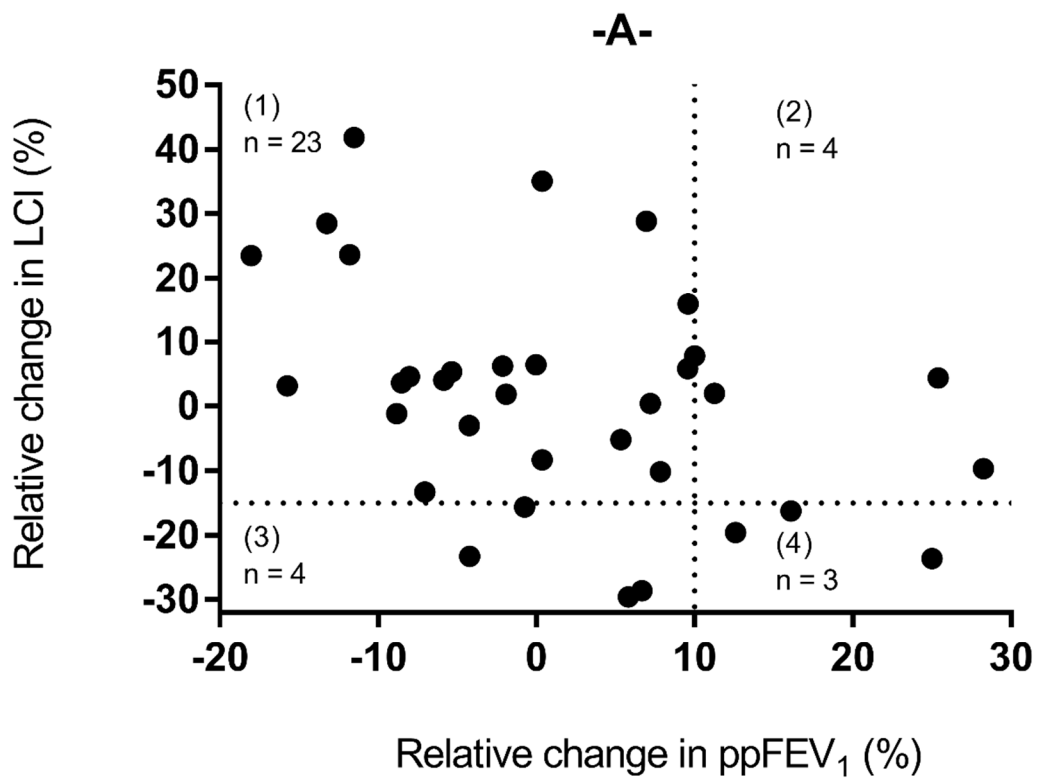
120 \*In the preceding year; BMI: body mass index; ppFEV<sub>1</sub>: percent predicted forced expiratory volume in  
 121 1 second; ppFVC: percent predicted forced vital capacity; LCI: lung clearance index; PI: pancreatic  
 122 insufficiency

123 **3.2 LCI variation over time**

124 LCI was measured at initiation and M6 or M12 or at all three time points in 34 (54%), 46 (73%) and 23  
 125 (36%) patients respectively (Table 2). At M6, there was a statistically insignificant absolute increase  
 126 (worsening) of 0.13±2.34 (95% CI: -0.68-0.95) units and a relative increase of 1.34±17.74% (95% CI: -  
 127 4.85-7.53) (p = 0.70). At M12, there was an insignificant mean relative change of 6.7±22.5% (95% CI: -  
 128 0.03-13.5) (p = 0.12). Absolute and relative changes of ppFEV<sub>1</sub> were +1.45% (95% CI: -1.4-4.3) and 1.8%  
 129 (95% CI: -2.2-5.8) at M6 (p = 0.62), and +2.09% (95% CI: -0.8-4.98) and 3.46% (95% CI: -0.95-7.87) at  
 130 M12 (p = 0.08).

131 **3.3 Concordance between LCI and ppFEV<sub>1</sub>**

132 A weak correlation was found between ppFEV<sub>1</sub> and LCI at both M6 (R = -0.358; P = 0.0374) and M12  
133 (R = -0.486; P=0.0006). As shown in **Figure 1**, relative changes of LCI vs. ppFEV<sub>1</sub> appeared  
134 heterogenous at M6 and M12. With a cut-off for relative change of 15% for LCI and 10% for ppFEV<sub>1</sub>  
135 as indicators of clinically relevant improvement, 76% and 70% of patients had concordant evolution  
136 of LCI and ppFEV<sub>1</sub> at M6 and M12 (Table 2). Discordant evolution was found in similar percentages at  
137 M6 and M12. For example, at M6, 4 patients (12%) showed improvement for ppFEV<sub>1</sub> but  
138 deterioration for LCI.



139

140



141 **Figure 1:** Correlations of relative changes between LCI and ppFEV<sub>1</sub> at M6 (A) or M12 (B). Dashed lines  
142 represent cut-off values for relative changes of ppFEV<sub>1</sub> and LCI (respectively set to 10 and 15%)  
143 chosen to define clinically relevant improvement. Quadrant (1): LCI stable or increased, ppFEV<sub>1</sub> stable  
144 or decreased; Quadrant (2): LCI stable or increased, ppFEV<sub>1</sub> stable or increased; Quadrant (3): LCI  
145 stable or decreased, ppFEV<sub>1</sub> stable or decreased, Quadrant (4): LCI stable or decreased, ppFEV<sub>1</sub> stable  
146 or increased. LCI increase means ventilation heterogeneity worsening.

147

148

1 **Table 2: LCI: Initial value and changes over time and concordance with ppFEV<sub>1</sub>**

LCI initial values and changes					
Initiation vs M6	<b>LCI at initiation</b>	<b>LCI at M6</b>	<b>Absolute change</b>	<b>Relative change</b>	<b>P value</b>
N = 34	12.8±3.5 (95% CI: 11.6-13.9)	12.9±4.0 (95% CI: 11.5-14.3)	0.13±2.34 (95% CI: -0.68-0.95)	1.34±17.74% (95% CI: -4.85-7.53)	0.70
Initiation vs M12	<b>LCI at initiation</b>	<b>LCI at M12</b>	<b>Absolute change</b>	<b>Relative change</b>	<b>P value</b>
N = 46	13.1±3.4 (95% CI: 12.1-14.1)	13.7±3.8 (95% CI: 12.5-14.8)	0.6±2.7 (95% CI: -0.21-1.40)	6.66±22.5% (95% CI: -0.03-13.5)	0.12
LCI and ppFEV <sub>1</sub> concordance					
At M6	<b>Concordant pairs</b>		<b>Discordant pairs</b>		
	→ or ↘ LCI	→ or ↗ LCI	→ or ↗ LCI	→ or ↘ LCI	
	→ or ↗ ppFEV <sub>1</sub> *	→ or ↘ ppFEV <sub>1</sub>	→ or ↗ ppFEV <sub>1</sub>	→ or ↘ ppFEV <sub>1</sub>	
N (%)	3 (9%)	23 (67%)	4 (12%)	4 (12%)	
At M12	<b>Concordant pairs</b>		<b>Discordant pairs</b>		
	→ or ↘ LCI	→ or ↗ LCI	→ or ↗ LCI	→ or ↘ LCI	
	→ or ↗ ppFEV <sub>1</sub> *	→ or ↘ ppFEV <sub>1</sub>	→ or ↗ ppFEV <sub>1</sub>	→ or ↘ ppFEV <sub>1</sub>	
N (%)	5 (11%)	27 (59%)	11 (24%)	3 (6%)	

2 \*Cut-offs for relative changes to define clinically relevant improvement were set at ±15% for LCI based on available data on relative changes (8-10) and at  
 3 ±10% for ppFEV<sub>1</sub>. Symbols: → or ↘ (stable or decreased); → or ↗ (stable or increased) with “stable” meaning a relative change below cut-off values.

## 1        **4. Discussion**

2        In this real-world observational study of lumacaftor-ivacaftor follow-up with a wide range of  
3        pulmonary function, we found no improvement in LCIs during the first year of treatment. We also  
4        found that LCI response to lumacaftor-ivacaftor was heterogenous.

### 5        **4.1 LCI response to lumacaftor/ivacaftor in real life**

6        In the present study, we found no significant changes in LCIs over time. These results do not align  
7        with other recently published results. Indeed, in a cohort of 49 patients, Shaw *et al.* reported a  
8        median LCI decrease (improvement) of 0.67 units (i.e., relative change of 5.9%) at M6 and 0.55 units  
9        (relative change of 4.3%) at M12. In their work, ppFEV<sub>1</sub> did not improve significantly at any time point  
10       (5). It is unlikely that the differences between the data of our study and those of Shaw *et al.* are due  
11       to the quality of the measurements as all involved centers had trained/qualified personnel for the  
12       tests and all traces were reviewed for quality control. The most likely explanation resides more so in  
13       marked differences between the study populations; despite similar ages, our patients had more  
14       severe disease and lower lung function (medians ppFEV<sub>1</sub> at 72.8% vs 91.3%).

### 15       **4.2 Concordance between LCI and ppFEV<sub>1</sub>**

16       With relative change cut-offs of 15% for LCI and 10% for ppFEV<sub>1</sub>, we found that about a third of  
17       patients had discordant evolution of both LCI and FEV<sub>1</sub>. The relative change cut-off of 15% for LCI was  
18       based on previous data obtained in preschool and school-aged children (8-10). Individual correlations  
19       of these two outcomes during CFTR modulator administration have never been reported to date, as  
20       these data are almost always reported at the group level. This heterogeneity has however been  
21       repeatedly reported during pulmonary exacerbation and the resulting data pooled for analysis by  
22       Sonneveld *et al.* That team reported an overall decrease in LCI of 0.4 units, but their LCI results were  
23       frequently discordant with ppFEV<sub>1</sub> whatever the cut-off used for relative change in LCI and FEV<sub>1</sub> (0, 5,

24 10 or 15%) (11). As a comparison, discordant results using cut-offs similar to ours represent 41.5%,  
25 which is higher than in our cases (28% and 30%).

#### 26 **4.3 Implication for using MBW in CF clinics: 1,2, 3...wait**

27 Some authors have raised the question of the use of MBW in clinics (12). Data are accumulating to  
28 show that this tool is particularly interesting in young children with milder lung disease. In patients  
29 with more severe pulmonary disease, as shown previously, measuring LCI did not bring added value  
30 to ppFEV<sub>1</sub> in two thirds of our cases. Because of discordant results in 30% of patients, interpretation  
31 will remain problematic for clinicians: Should more weight be put on LCI for decision making when  
32 FEV<sub>1</sub> increases and LCI worsens? Should clinicians be reassured by an improvement of LCI when FEV<sub>1</sub>  
33 deteriorates? Although imaging studies have contributed to a better understanding of LCI  
34 heterogeneity, these and other questions do remain (13).

#### 35 **4.4 Limitations**

36 The work we present here does have several limitations. Firstly, only a small percentage (7.5%) of the  
37 initial cohort could be enrolled in it. Secondly, only a third of our patients had data for all three of the  
38 time points considered in the study. Thirdly, ideally the study would only have included MBW  
39 measurements from clinically stable clinic visits. However, it was not possible to retrospectively  
40 determine the clinical status of participants and this may have contributed to the observed  
41 heterogeneity. Finally, patient's adherence to treatment was not monitored. Lack of the observed  
42 treatment effect could also be related to poor adherence even if real life results have shown good  
43 adherence to Lumacaftor-Ivacaftor in adolescents 6 and 12 months after initiation (14).

#### 44 **4.5 Conclusion**

45 We found that LCI nor FEV<sub>1</sub> did not decrease after one year of exposure to lumacaftor/ivacaftor in  
46 adolescents with CF. Individual LCI and FEV<sub>1</sub> changes at 6 and 12 months showed discordance in

47 around a third of our patients. These results suggest that the MBW test may be a more useful  
48 monitoring tool for individuals with early cystic fibrosis lung disease.

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8 Mely (Giens); Boubou Camara, Catherine Llerena, Isabelle Pin, Sébastien Quétant (Grenoble); Aurélie  
9 Cottereau, Antoine Deschildre, Alice Gicquello, Thierry Perez, Lidwine Stervinou-Wemeau, Caroline  
10 Thumerelle, Benoit Wallaert, Nathalie Wizla (Lille); Jane Languepin, Céline Ménétrez, Magalie Dupuy-  
11 Grasset (Limoges); Lucie Bazus, Clelia Buchs, Virginie Jubin, Marie-Christine Werck-Gallois, Catherine  
12 Mainguy, Thomas Perrin, Philippe Reix, Agnès Toutain-Rigolet (Lyon Pédiatrie); Isabelle Durieu,  
13 Stéphane Durupt, Quitterie Reynaud, Raphaelle Nove-Josserand (Lyon adultes); Melisande Baravalle-  
14 Einaudi, Bérangère Coltey, Nadine Dufeu, Jean-Christophe Dubus, Nathalie Stremler (Marseille);  
15 Davide Caimmi, Raphaël Chiron (Montpellier); Yves Billon, Jocelyne Derelle, Sébastien Kieffer, Anne-  
16 Sophie Pichon, Cyril Schweitzer, Aurélie Tatopoulos (Nancy); Sarah Abbes, Tiphaine Bihouée, Isabelle  
17 Danner-Boucher, Valérie David, Alain Haloun, Adrien Tissot (Nantes); Sylvie Leroy, Carole Bailly-  
18 Piccini (Nice); Annick Clément, Harriet Corvol, Aline Tamalet (Paris, Trousseau); Pierre-Régis Burgel,  
19 Isabelle Honoré, Dominique Hubert, Reem Kanaan, Clémence Martin (Paris, Cochin); Cécile Bailly,  
20 Frédérique Chédevergne, Jacques De Blic, Brigitte Fauroux, Murielle Le Bourgeois, Isabelle Sermet-  
21 Gaudelus (Paris, Necker); Bertrand Delaisi, Michèle Gérardin, Anne Munck (Paris, Robert Debré);  
22 Michel Abély, Bruno Ravoninjatovo (Reims); Chantal Belleguic, Benoit Desrues, Graziella Brinchault  
23 (Rennes); Michel Dagorne, Eric Deneuville, Sylvaine Lefeuvre (Rennes-Saint Briec); Anne Dirou, Jean  
24 Le Bihan, Sophie Ramel (Roscoff); Stéphane Dominique, Christophe Marguet (Rouen); Annabelle  
25 Payet (La Réunion); Romain Kessler, Michele Porzio, Vincent Rosner, Laurence Weiss (Strasbourg);  
26 Sandra de Miranda, Dominique Grenet, Abdoul Hamid, Clément Picard (Suresnes); François Brémont,  
27 Alain Didier, Géraldine Labouret, Marie Mittaine, Marlène Murriss-Espin, Laurent Têtu (Toulouse);  
28 Laure Cosson, Charlotte Giraut, Anne-Cécile Henriot, Julie Mankikian, Sophie Marchand (Tours);  
29 Sandrine Hugé, Véronique Storni (Vannes); Emmanuelle Coirier-Duet (Versailles).

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