



**HAL**  
open science

## Feasibility and efficacy of combined pancreatic islet-lung transplantation in cystic fibrosis-related diabetes–PIM study: A multicenter phase 1–2 trial

Luc Rakotoarisoa, Clothilde Wagner, Marion Munch, Benjamin Renaud Picard, Dominique Grenet, Anne Olland, Michel Greget, Iulian Enescu, Florence Bouilloud, Pierre Bonnette, et al.

### ► To cite this version:

Luc Rakotoarisoa, Clothilde Wagner, Marion Munch, Benjamin Renaud Picard, Dominique Grenet, et al.. Feasibility and efficacy of combined pancreatic islet-lung transplantation in cystic fibrosis-related diabetes–PIM study: A multicenter phase 1–2 trial. *American Journal of Transplantation*, 2022, 22 (7), pp.1861-1872. 10.1111/ajt.17058 . hal-04176576

**HAL Id: hal-04176576**

**<https://hal.science/hal-04176576v1>**

Submitted on 21 Jun 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.





L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

## ORIGINAL ARTICLE

# Feasibility and efficacy of combined pancreatic islet-lung transplantation in cystic fibrosis-related diabetes–PIM study: A multicenter phase 1–2 trial

Luc Rakotoarisoa<sup>1,2</sup> | Clothilde Wagner<sup>1</sup> | Marion Munch<sup>1</sup> | Benjamin Renaud Picard<sup>2,3</sup>  |  
 Dominique Grenet<sup>4</sup> | Anne Olland<sup>2,5</sup> | Michel Greget<sup>6</sup> | Iulian Enescu<sup>6</sup> |  
 Florence Bouilloud<sup>7</sup> | Pierre Bonnette<sup>8</sup> | Axel Guth<sup>9</sup> | Domenico Bosco<sup>10</sup> |  
 Catherine Mercier<sup>11,12,13,14</sup> | Muriel Rabilloud<sup>11,12,13,14</sup> | Thierry Berney<sup>10</sup>  |  
 Pierre Yves Benhamou<sup>15</sup> | Gilbert Massard<sup>2,5</sup> | Coralie Camilo<sup>11,12,13,14</sup> |  
 Cyrille Colin<sup>11,12,13,14</sup> | Cécile Arnold<sup>16</sup> | Romain Kessler<sup>2,3</sup>  | Laurence Kessler<sup>1,2</sup>  |  
 on behalf of the GRAGIL-TREPID Group

<sup>1</sup>Department of Endocrinology, Diabetes and Nutrition, Strasbourg University Hospital, France

<sup>2</sup>Inserm UMR 1260, Regenerative Nanomedicine, Strasbourg, France

<sup>3</sup>Department of Pneumology, Cystic Fibrosis Center, Strasbourg University, Strasbourg, France

<sup>4</sup>Department of Pneumology, Cystic Fibrosis Center, Hôpital Foch, Suresnes, France

<sup>5</sup>Department of Thoracic Surgery, Strasbourg University Hospital, Strasbourg, France

<sup>6</sup>Department of Radiology, Strasbourg University Hospital, Strasbourg, France

<sup>7</sup>Department of Endocrinology, Hôpital Foch, Suresnes, France

<sup>8</sup>Department of Thoracic Surgery, Hôpital Foch, Suresnes, France

<sup>9</sup>Department of Radiology, Hôpital Foch, Suresnes, France

<sup>10</sup>Department of Surgery, Islet Isolation, and Transplantation, Geneva University Hospitals, Geneva, Switzerland

<sup>11</sup>Pôle Santé Publique, Service de Biostatistique et Bioinformatique, Hospices Civils de Lyon, Lyon, France

<sup>12</sup>Université de Lyon, Lyon, France

<sup>13</sup>Université Lyon 1, Villeurbanne, France

<sup>14</sup>Laboratoire de Biométrie et Biologie Évolutive, Équipe Biostatistique-Santé, CNRS, UMR 5558, Villeurbanne, France

<sup>15</sup>Department of Endocrinology, Diabetes and Nutrition, Grenoble University Hospital, Grenoble, France

<sup>16</sup>Department of Clinical Research, Strasbourg University Hospital, Strasbourg, France

## Correspondence

Laurence Kessler, Service  
 d'Endocrinologie, Diabète et Nutrition,  
 Hôpitaux Universitaires de Strasbourg,  
 Hôpital Civil, UMR Inserm 1260,  
 Nanomedicine Regenerative, 1 place de  
 l'Hôpital, 67000 Strasbourg, France.  
 Email: [laurence.kessler@chru-strasbourg.fr](mailto:laurence.kessler@chru-strasbourg.fr)

Cystic fibrosis-related diabetes (CFRD) is a common complication of cystic fibrosis (CF), and restoring metabolic control in these patients may improve their management after lung transplantation. In this multicenter, prospective, phase 1–2 trial, we evaluate the feasibility and metabolic efficacy of combined pancreatic islet-lung transplantation from a single donor in patients with CFRD, terminal respiratory failure, and poorly controlled

**Abbreviations:** AUC, area under the curve; CF, cystic fibrosis; CFRD, cystic fibrosis-related diabetes; CGM, continuous glucose monitoring; FEV1, forced expired volume in one second; FVC, forced vital capacity; HRQL, health-related quality of life; IEQ, islet equivalent; PIM, greffe Poumon Ilots dans la Mucoviscidose; SAEs, serious adverse events; TAR, time above the range; TBR, time below the range; TIR, time in range.

ClinicalTrials.gov Identifier: NCT01548729.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *American Journal of Transplantation* published by Wiley Periodicals LLC on behalf of The American Society of Transplantation and the American Society of Transplant Surgeons.

**Funding information**

French Ministry of Health, Programme Hospitalier de Recherche Clinique 2011., Grant/Award Number: PHRC-N°2010 - HUS n°4790; French patient association VLM (Vaincre La Mucoviscidose).

diabetes. Islets were infused via the portal vein under local anesthesia, 1 week after lung transplantation. At 1 year, the primary outcome was transplant success as evaluated by a composite score including four parameters (weight, fasting glycemia, HbA1c, and insulin requirements). Ten participants (age: 24 years [17–31], diabetes duration: 8 years [4–12]) received a combined islet-lung transplant with 2892 IEQ/kg [2293–6185]. Transplant success was achieved in 7 out of 10 participants at 1-year post transplant. Fasting plasma C-peptide increased from 0.91 µg/L [0.56–1.29] to 1.15 µg/L [0.77–2.2], HbA1c decreased from 7.8% [6.5–8.3] (62 mmol/mol [48–67]) to 6.7% [5.5–8.0] (50 mmol/mol [37–64]), with 38% decrease in daily insulin doses. No complications related to the islet injection procedure were reported. In this pilot study, combined pancreatic islet-lung transplantation restored satisfactory metabolic control and pulmonary function in patients with CF, without increasing the morbidity of lung transplantation.

**KEYWORDS**

cystic fibrosis, islet transplantation, lung transplantation, respiratory failure, secondary diabetes

## 1 | INTRODUCTION

Cystic fibrosis (CF) is one of the most common inherited autosomal recessive diseases within the Caucasian population, with an incidence of 1:4000 births. It is a channelopathy, arising from mutations in the gene encoding for the CF transmembrane conductance regulator (CFTR), responsible for a range of multivisceral disorders (pulmonary, hepatic, pancreatic endocrine/exocrine, and infertility), dominated by pulmonary involvement.

Despite optimized medical therapy, more than 95% of affected individuals ultimately die from respiratory failure.<sup>1</sup> At this stage, lung transplantation represents the final treatment option. In 2019, adult CF patients who underwent primary lung transplantation had a median survival of 9.2 years, with a survival rate of 92.3% at 1 year and 63.1% at 5 years.<sup>2</sup> Improvement in pulmonary and nutritional management has considerably improved patient survival, which is currently 40–50 years old.<sup>3</sup> The prevalence of cystic fibrosis-related diabetes (CFRD), a common complication of CF, increases with age, reaching an incidence of 40%–50% in adults.<sup>4</sup> Diabetes-related excess mortality is observed within cohorts of CF patients across all age groups.<sup>5</sup> Diabetes is also a major risk factor for pulmonary dysfunction,<sup>6</sup> increasing the risk of respiratory decline by a factor of 1.8,<sup>7</sup> and is equally associated with poorer nutritional status.<sup>8</sup>

For patients requiring lung transplantation, CFRD increases posttransplant morbidity and mortality.<sup>9,10</sup> The presence of CFRD before transplantation decreases patient survival, while promoting infection and posttransplant pulmonary rejection.<sup>11,12</sup> In posttransplant patients, the prevalence of diabetes was shown to increase, mainly due to the diabetogenic effect of immunosuppressive treatments.<sup>13</sup> For patients with sufficient endogenous insulin production, lung transplantation can improve glycemic control by decreasing insulin resistance.<sup>14</sup> On the other hand, for patients who have low

endogenous insulin production, and for whom optimized insulin treatment does not allow satisfactory glycemic control, pulmonary transplantation may lead to a major glycemic imbalance with a harmful impact on the pulmonary graft.

Several centers worldwide have performed pancreatic islet allotransplantations for the treatment of type 1 diabetes patients, who have a high glucose variability with hypoglycemia unawareness and/or functioning kidney transplantation.<sup>15–18</sup> These studies reported that islet transplantation was an efficient treatment, able to dramatically improve both short- and long-term metabolic outcomes with very low morbidity. By restoring metabolic control, islet transplantation may improve the management of patients with CFRD undergoing lung transplant and decrease the complication rate in the early postoperative period. However, thus far, only case reports have been published, and questions remain as to the efficacy and safety of this procedure in this particular patient population.<sup>19,20</sup>

Therefore, the primary objective of the present study was to evaluate the feasibility and metabolic efficacy of combined islet-lung transplantation from the same donor, in the postoperative period and in the medium term, at 1-year follow-up. The secondary objectives were to evaluate lung function, quality of life, and the tolerance of this technique.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and participants

This study was a prospective open-label, multicenter, phase 1–2 trial, involving four University Hospitals in France (Strasbourg, Suresnes, Lyon, Grenoble) and one islet preparation unit in Switzerland (Geneva).

Eligible patients attending lung transplant centers for pretransplant evaluation were consecutively recruited to the study if they met the following inclusion criteria: (i) subject aged  $\geq 14$  years old; (ii) diagnosis of CF based on clinical features and on positive CF genotype; (iii) terminal respiratory failure requiring lung transplantation; (iv) CFRD progressing for more than 3 years, requiring insulin therapy with at least three daily insulin injections or an insulin pump; (v) fasting basal C-peptide  $< 0.5$   $\mu\text{g/L}$  and/or an insufficient response in C-peptide to the glucagon test, defined by the stimulated C-peptide:basal C-peptide ratio of  $< 2$ ; and (vi) HbA1c  $> 7\%$  and/or mean amplitude of glycemic excursion (MAGE)  $> 1.25$  according to continuous glucose monitoring for patients with anemia/undernutrition. Exclusion criteria were (i) persistent elevation of liver enzymes at enrollment (ASAT, ALAT, PAL, or total bilirubin  $> 3\times$  the upper limit of normal); (ii) cirrhosis; (iii) portal hypertension; (iv) patient with heart, liver, or kidney transplantation; and (v) a record of poor therapeutic compliance. A committee composed of investigators from at least half of the study centers reviewed each patient's suitability for islet transplantation. A multidisciplinary independent committee subsequently validated the enrollment of patients. The patients were enrolled in the study when they were placed on the islet-lung transplant waiting list. After 1 year of follow-up of the first five patients, an independent study monitoring committee composed of experts in pancreatic islet transplantation, lung transplantation, pharmacovigilance, and biostatistics decided whether to stop or continue the study. These interim analyses were repeated for each consecutive group of five patients.

This study was approved by the French Committee for the Protection of Persons Participating in Biomedical Research (approval number CPP Est IV: 11/10), and clinical trial authorization was obtained from the French National Competent Authority (TC296A, N° EudraCT: 2011-001941-33). Written informed consent was obtained from all patients. ClinicalTrials.gov Identifier number was: NCT01548729.

## 2.2 | Procedures

Patients assigned to pancreatic islet-lung transplantation were immediately registered on the national pancreatic islet-lung transplantation waiting list. Both organs were assigned to a given patient according to ABO blood type compatibility, morphometric data for lung transplantation, and after a negative crossmatch. Bi-pulmonary block and pancreas were obtained from brain-dead, multi-organ donors procured through the Swiss Transplant Agency and French Biomedicine Agency. Both organs were recovered from the same donor by two separate surgical teams. Donor criteria for lung and pancreas acceptability were the usual criteria used for lung and islet transplantation.<sup>21,22</sup> The bi-pulmonary block was transplanted according to standard operating techniques: bilateral sequential lung transplant by transverse sternobithoracotomy.<sup>23</sup> In parallel, the pancreas was sent to the Laboratory of Cell Isolation and Transplantation (Geneva) for islet isolation and purification according

to a modified version of the method previously described.<sup>24</sup> After tissue collection, islets were purified by centrifugation in continuous Biocoll density gradients (Biochrom KG, Berlin, Germany) using a COBE 2991 cell processor (Cobe, Lakewood, CO). The pancreatic islets were maintained in a culture medium (CMRL 1066 without phenol red [Sigma-Aldrich]), supplemented in human AB serum for a maximum of 10 days. Patients were scheduled to receive a minimum of 100,000 IEQs (islets equivalent) in one infusion. To avoid non-optimal transplantation conditions, patients received lung transplantation alone in the following situations: (i) severe, unstable, and rapidly evolving pulmonary state, requiring an urgent lung transplantation but unsuitability of the donor pancreas; (ii) insufficient number of isolated islets ( $< 100,000$  IEQ); and (iii) unstable clinical condition after lung transplantation, for example, severe life-threatening infection, precarious respiratory status, unstable hemodynamic status, major hemostasis disorder, and intraperitoneal effusion. When patients reached hemodynamic stability, the islets were infused, under local anesthesia, via percutaneous transhepatic portal vein catheterization under angiographic control.

## 2.3 | Immunosuppression protocol and concomitant treatments

The immunosuppression protocol was established by a consensus between the four participating teams, taking into account current data from the International Lung Transplant Registry,<sup>2</sup> and the establishment of corticosteroid therapy at the minimum optimal dose, allowing both control of pulmonary rejection and reducing damage to the transplanted islets. A detailed immunosuppression protocol can be found in the Supporting Information. In brief, patients received a loading dose of IV methylprednisolone before induction of anesthesia, followed by additional doses after lung implantation, on day 1 following transplantation (D1), and at D2. Basiliximab was given at D0 and D4. Maintenance immunosuppressive therapy was introduced, comprising oral prednisolone, tacrolimus, and mycophenolate mofetil.

Prophylactic anticoagulation was carried out prior to lung transplantation and halted 6 h before islet transplantation. Following islet transplantation, heparin therapy was resumed intravenously for 48 h, then subcutaneously for 5 days using low-molecular-weight heparin.

During the postoperative period, insulin was administered via pump or injection, and doses adapted through self-monitoring or by means of a continuous glucose monitoring (CGM) system.

## 2.4 | Study outcomes

The primary outcome was the metabolic efficacy of the combined islet-lung transplantation, measured by a composite score including metabolic and nutritional parameters. The transplant was defined as successful if three of the following four criteria were reached at

1-year follow-up: weight increase of  $\geq 5\%$  compared to baseline; fasting plasma glucose (ADVIA 2400 Clinical Chemistry analyzer, Siemens Healthcare SAS),  $< 110$  mg/dl;  $\geq 30\%$  reduction in insulin requirements compared to baseline;  $\geq 0.5\%$  decrease in HbA1c in absolute terms (high-performance liquid chromatography, Bio-Rad) compared to baseline. Initially, the primary outcome of our study was the metabolic efficiency of islet-lung transplantation, measured by a metabolic parameter ( $\Delta$ C-peptide) defined as the ratio of C-peptide (Eleclys C-Peptide immunochemical luminescence measurement kit and Cobas 6000 analyzer, Roche Diagnostics) at 6 min after intravenous injection of 1-mg glucagon, to C-peptide measured at the basal level. This ratio is, therefore, a direct marker of the function of transplanted islets. As endogenous insulin secretion is partially preserved in CFRD, the success of the graft was defined by  $\Delta$ C-peptide  $> 2$ . Interim analysis of the first five patients by the independent monitoring committee showed that none of the patients reached this primary end point, despite four out of five patients showing a metabolic benefit of the transplant based on markers of glycemic control. On the proposal of the independent monitoring committee, and after validation of the amendment to the protocol, the primary end point was modified to the measurement of metabolic efficiency by the new composite score.

Key secondary outcomes were BMI ( $\text{kg}/\text{m}^2$ ), HbA1c (%), fasting C-peptide ( $\mu\text{g}/\text{L}$ ), fasting plasma glucose ( $\text{mg}/\text{dl}$ ), and insulin requirements ( $\text{IU}/\text{kg}/\text{day}$ ), which were evaluated every 3 months during the 1-year period of follow-up. Due to a lack of availability of CGM devices, only six patients underwent continuous glucose measurements to evaluate the time in the range (TIR, 70–140 mg/dl and 70–180 mg/dl), time below the range (TBR,  $< 70$  mg/dl), and time above the range (TAR,  $> 140$  mg/dl and  $> 180$  mg/dl) 1 year after transplantation. Lung function was measured by spirometry tests, which were carried out every 3 months, including FEV1 and FVC measurements (Vmax spirometer, VIASYS, Healthcare Respiratory Technologies), adjusted in percentage according to age, gender, height, and weight. Health-related quality of life (HRQL) was assessed with the 36-item Short-Form Health Survey (SF-36),<sup>25</sup> the Diabetes Quality of Life (DQOL) questionnaire,<sup>26</sup> and the Cystic Fibrosis Questionnaire 14+ (CFQ14+),<sup>27</sup> at baseline, 6 months, and 1 year after combined islet-lung transplantation. All scores range from 0 to 100, with a higher score indicating a better quality of life. Questionnaires were sent and collected by post, by the Pole IMER at the University Hospital of Lyon.

## 2.5 | Adverse events

All serious adverse events (SAEs) during the procedure and follow-up period were recorded using the System Organ Class in the medical dictionary for regulatory activities and analyzed.<sup>28</sup> The independent data and safety monitoring board was informed of all SAEs and was authorized to recommend suspension or early termination of the trial. Adverse events (AEs) were monitored (and classified as being most likely related to the islet transplantation procedure, immunosuppression, and/or lung transplantation surgical procedure), as well as the number of pulmonary rejection episodes (requiring or not,

corticosteroid boluses), the number of hospitalization days for the transplantation procedure, and during the follow-up period.

## 2.6 | Statistical analysis

Analysis of the primary outcome was carried out using Bayesian sequential analysis,<sup>29</sup> carried out every five patients. Prior knowledge on the probability of success set at 60%, based on the opinion of three experts, was combined with the information given by historical data (four successful outcomes in five transplanted patients). This prior information was described by a beta distribution with parameter values ( $\alpha = 4.6$ ,  $\beta = 2.15$ ), equivalent to adding approximately seven patients to the observed data and corresponds to approximately five transplant successes and two failures. The probability of success judged clinically pertinent and that judged insufficient was set at 50% and 20%, respectively. It was determined that for an intervention efficacy of 55%, the enrollment of 15 patients would allow to conclude a probability of success  $> 50\%$  with a probability of 80%. However, for a probability of success of 15%, the probability that the study concluded with an insufficient efficacy was low (12%).

Two interim analyses were carried out after the enrollment and follow-up of 5 and 10 patients. The parameters of the posterior beta distribution were obtained by the addition of the observed successes and failures to the parameters of the prior distribution. This allowed to estimate the probability of success and its 95% credibility interval and the posterior probabilities that the probability of success was  $> 50\%$  and lower than 20% respectively. The trial was stopped for efficacy at the second interim analysis. No correction was applied for multiple testing. Sensitivity analyses were performed, ignoring firstly, the prior information based on experts' opinion, and secondly, the prior information based on experts' opinion and historical data.

Median and interquartile ranges (IQR) were used to describe the changes in metabolic respiratory and quality of life parameters during the period between enrollment and 12-month follow-up.

Bayesian analysis was carried out using R version 4.02. Descriptive analysis and analysis of secondary outcomes were carried out using SAS version 9.4.

## 3 | RESULTS

### 3.1 | Patient characteristics

From February 25, 2012 to December 20, 2019, 14 patients were enrolled (4 males/10 females) and 10 patients received combined islet-lung transplantation. One patient was withdrawn from the transplant waiting list due to satisfactory pulmonary clinical evolution. Three patients initially enrolled in the study received lung transplantation alone, due to an urgent need for lung transplantation, but unsuitability of the donor pancreas (required criteria not met in one case and an insufficient number of isolated islets in the other two cases). The characteristics of the remaining 10 patients,

who received combined islet-lung transplantations, are specified in Table 1. Before the combined islet-lung transplant, seven patients were treated with an external insulin pump and three patients with multiple insulin injections. A median of 2892 IEQ/kg [IQR: 5.8–7.6] was infused, having been cultured for 4.5 days [3–7], with a purity of 50% [35–70]. Characteristics of the three patients who underwent lung transplantation only are given in the Supporting Information (Table S1).

### 3.2 | Primary outcome

The composite score determined successful transplantation in 7 out of 10 patients at 1-year follow-up (Figure 1, Table S2). The posterior probability that the efficacy is >50% was 95%, and the posterior probability that the efficacy is lower than 20% was 0.0007%. The probability of success was estimated at 69% (95% credibility interval, 95 CI: 46%–88%). Sensitivity analyses did not substantially alter the results when ignoring the prior information based on experts' opinion (estimated probability of success: 70%; 95 CI: 46%–89%), nor when ignoring the prior information based on experts' opinion and historical data (estimated probability of success: 67%; 95 CI: 39%–89%). Among the three failed patients (Patients 4, 6, and 9), one patient presented severe lung rejection (Grade A3) and had insufficient metabolic control due to therapeutic non-compliance, with an irregular oral intake of drugs and repeated discontinuation of insulin therapy. The second patient received the fewest islets (1550 IEQ/kg). No events related to metabolic failure were identified for the third patient. Based on the composite score, transplant success was achieved in one out of three lung only transplanted patients at 1 year (Table S3).

### 3.3 | Secondary outcomes

The functionality of islets was confirmed 1 year after transplantation by a median increase in plasma C-peptide from 0.91 µg/L [0.56–1.29] at baseline to 1.15 µg/L [0.77–2.2] (Table S4). Blood glucose control was improved, as shown by the decrease in HbA1c from 7.8% [6.5–8.3] (62 mmol/mol [48–67]) to 6.7% [5.5–8.0] (50 mmol/mol [37–64]), and a decrease in fasting blood glucose from 135 mg/dl [95–140] to 105 mg/dl [102–108]. Daily insulin requirements decreased by 38%, from 0.65 IU/kg/day [0.21–1.74] to 0.45 IU/kg/day [0.00–1.14] (Figure 1, Table S2). After transplant, among the seven patients using an insulin pump, six continued their treatment and one patient replaced the insulin pump with multiple insulin injections. Among the three patients treated with multiple insulin injections, one (Patient 10) stopped insulin entirely, and the two others continued their treatment.

CGM data were available for six patients (Patients 2, 3, 4, 5, 6, and 7). These patients showed an improvement in glycemic control over 1 year of follow-up, with an increase in TIR from 32% [29–49] to 56% [42–67] and from 66% [46–76] to 86% [57–89] for the ranges

70–140 mg/dl and 70–180 mg/dl, respectively (Figure 2). Average glucose level per day also decreased, from 165 mg/dl [129–184] to 136 mg/dl [125–146]. TIR (70–140 mg/dl) was improved for all patients except for Patient 4, whose composite score determined transplantation failure. Coefficient of variation decreased from 39% [17–56] at enrollment to 35% [63–62] 1 year after islet-lung transplantation.

An improvement in nutritional parameters was observed, by a median increase in BMI from 18.9 kg/m<sup>2</sup> [16.6–19.6] to 20.3 kg/m<sup>2</sup> [17.0–24.0] (Figure 1) and in albuminemia from 32 g/L [21–41] to 44 g/L [26–47]. Respiratory parameters were also improved, with an increase in FEV1 from 24% [13–28] to 71% [67–80] and in FVC from 41% [33–55] to 78% [63–88] (Figure 3). Improvement in respiratory function was equally observed in the three patients receiving lung transplantation only (Table S5).

### 3.4 | Health-related quality of life (HRQL)

At 1-year follow-up, SF-36 questionnaire analysis showed improvements in the parameters of physical functioning, role limitations—physical, bodily pain, general perceptions of health, vitality, and emotional role limitations (Table S6). No variation was observed regarding social functioning, while the mental health score increased slightly from 44 [40–51] to 47 [38–57]. The Physical Component Score increased from 28 [21–45] to 54 [46–56], while the Mental Component Score remained stable at 51 [37–55] versus 53 [40–54]. In the DQOL questionnaire, satisfaction, impact of diabetes, and social worry improved slightly, while diabetes-related worry was unchanged. All parameters measuring HRQL improved in the CFQ14+ questionnaire, with the exception of emotion which remained stable, and digestive problems which were shown to worsen. Health perception improved, from a score of 18 [9–36] to 72 [45–100]. These improvements were observed from month 6 of follow-up onward.

### 3.5 | Safety

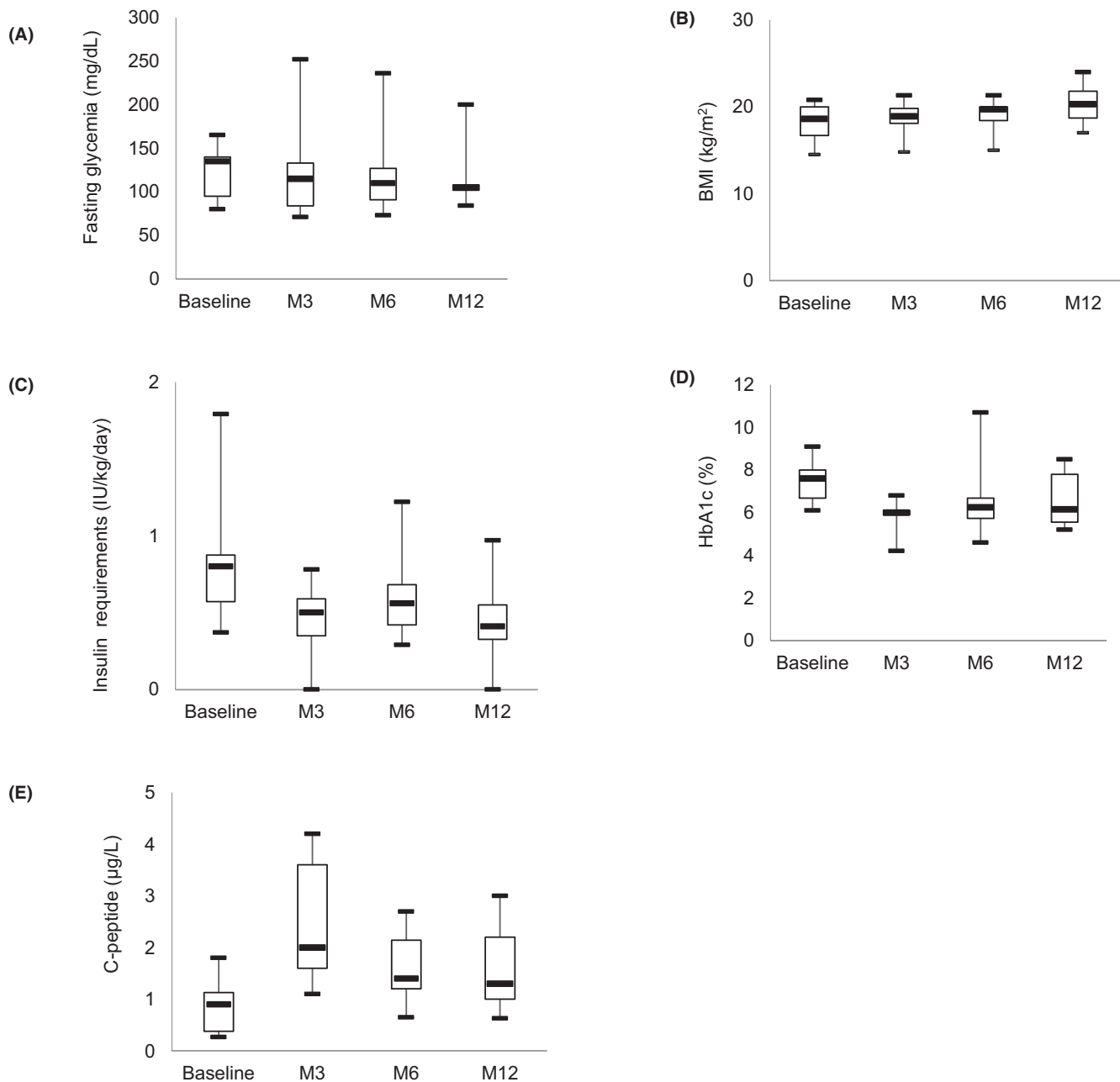
No death or loss of lung transplant was observed during the 1-year follow-up. Among the 296 AEs (229 non-serious and 67 SAEs) reported during follow-up, 45% occurred within the 1st month (Table 2). Fifty-four percent of SAEs were reported within the 1st month. No complications related to the islet injection procedure were reported. The main SAEs were lung infection and respiratory, mediastinal, and vascular disorders. All reported AEs and SAEs were expected, and all resolved without sequelae. Six patients developed acute cellular lung rejection without the presence of donor-specific antibodies. Among the nine Grade A1 lung graft rejections, seven required simple monitoring without corticosteroid treatment, and two required bolus steroid treatment. The median length of hospitalization for islet-lung transplantation was 34 days [25–37]. Ten readmissions were reported during the 1-year follow-up: acute renal failure secondary to diarrhea ( $n = 3$ ), pulmonary

TABLE 1 Characteristics of CF patients and islet grafts before islet-lung transplantation

Patient											Median [IQR]
	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	
Sex	F	F	F	M	M	F	F	F	F	M	n/a
Age	16	35	22	35	27	41	21	21	20	35	24 [17-31]
Mutation	ΔF508-/-	ΔF508-/-	W1282X-/-	ΔF508-/-	ΔF508-/-	ΔF508-/-	ΔF508-/-	ΔF508-/-	ΔF508-/-	ΔF508-/-	n/a
Age at CF diagnosis (years)	4	1	0	4	0	7	0	3	0	1	1 [0-4]
Diabetes duration (years)	3	12	4	12	10	25	8	4	5	8	8 [4-12]
BMI (kg/m <sup>2</sup> )	20.7	19.7	19.3	21.3	17.3	18.6	14.5	19.1	16.3	15.6	18.9 [16.6-19.36]
Fasting glycemia (mg/dl)	149	128	133	135	137	164	80	94	86	138	134 [103-138]
HbA1c (%)	6.5	8.3	5.8	8.8	8.2	7.5	6.5	9.1	6.5	8.1	7.8 [6.5-8.3]
C-peptide (μg/L)	1.8	0.52	1.4	0.97	0.32	1.6	0.68	0.92	0.33	0.89	0.91 [0.56-1.29]
Insulin requirement (IU/kg/day)	0.7	0.5	0.4	0.2	0.7	0.6	0.6	1.7	1.1	1.9	0.65 [0.21-1.74]
FEV1 (% predicted)	22	29	21	29	29	17	25	26	13	18	24 [19-28]
FVC (% predicted)	38	55	32	58	76	44	53	34	17	27	41 [33-55]
Total IEQ	513,750	245,339	100,183	100,792	110,083	124,292	314,417	229,000	243,875	278,333	236,438 [110,083-278,333]
IEQ per kg	8422	2708	1680	1550	2293	2645	8734	3075	5672	6185	2892 [2293-6185]
Islet culture duration (day)	3	3	5	4	6	3	2	8	8	7	4.5 [3-7]
Islet purity (%)	73	31	35	31	77	43	47	53	70	66	50 [35-70]

Abbreviations: -/-, homozygous mutation; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IEQ, islet equivalent; n/a, not applicable.





**FIGURE 1** Metabolic results at baseline and 3 (3 M), 6 (6 M), and 12 (12 M) months after combined islet-lung transplantation: (A) fasting glycemia, (B) BMI, (C) insulin requirements, (D) HbA1c, and (E) plasma C-peptide. Results are expressed as boxplots with median, minimum, maximum values and IQR

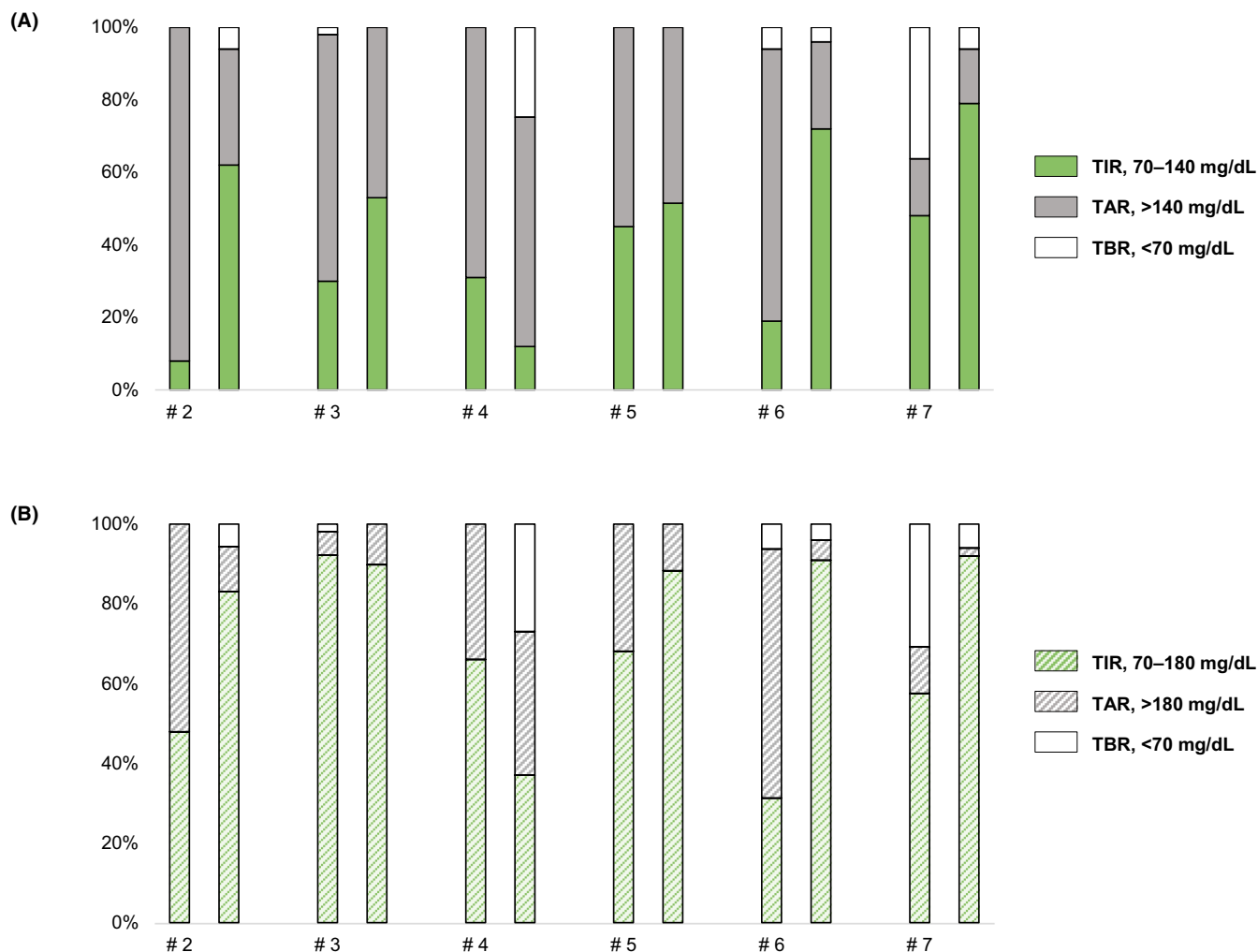
infection ( $n = 2$ ), cytomegalovirus infection with ileocolitis ( $n = 2$ ), heart rhythm disorder ( $n = 1$ ), left heart failure ( $n = 1$ ), and psychiatric disorder ( $n = 1$ ).

#### 4 | DISCUSSION

In this pilot study, we demonstrate the efficacy and feasibility of combined pancreatic islet-lung transplantation in CF patients with end-stage respiratory failure and CFRD. Following lung transplantation, diabetes promotes the development of complications, such

as acute rejection, severe infection, and renal failure, which justifies careful monitoring and aggressive management in these patients.<sup>30</sup> For the patients enrolled in our study, the purpose of islet transplantation was not to reverse diabetes, but to restore satisfactory glucose control, aiming to improve clinical management during the postoperative period and in the medium term. After 1 year of follow-up, the majority of grafted patients displayed satisfactory metabolic control and an improvement in lung function. For these patients, all parameters of metabolic control had improved, with a decrease in HbA1c, a reduction in exogenous insulin needs, an increase in continuous glucose-monitored TIR, together with an increase in C-peptide





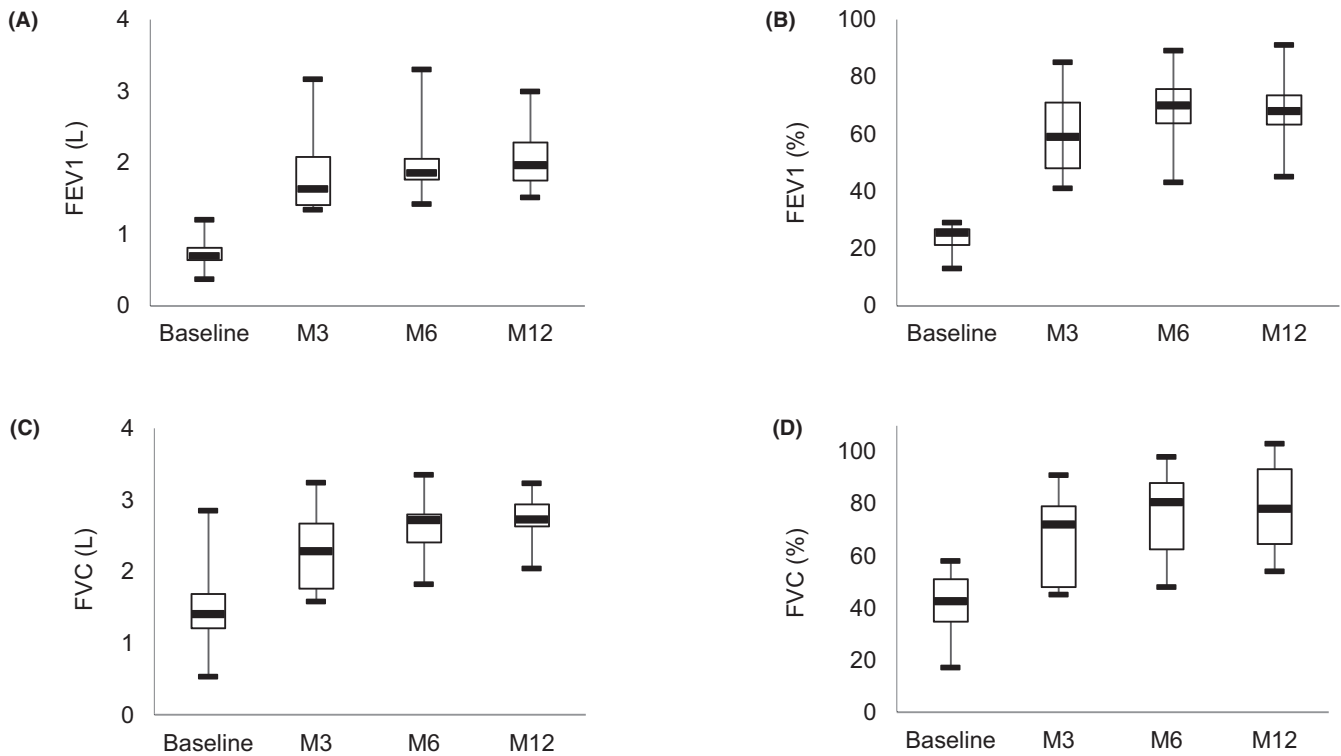
**FIGURE 2** CGM data at baseline and 1 year after combined lung-islet transplantation. For each participant, CGM data are shown at baseline (left column) and at 1-year follow-up (right column). Presentation of data using (A) the more stringent TIR employed for the composite score of this study (70–140 mg/dl) and (B) the standard TIR (70–180 mg/dl). The percentage of time spent in different glycemic ranges is indicated by different shades of gray according to the key. CGM, continuous glucose measurement; TIR, time in range; TAR, time above range; TBR, time below range; #, patient number [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

after 1 year of follow-up. For those patients who did not achieve satisfactory metabolic control, non-compliance with treatment and insufficient quantity of islets provide possible explanations, while one patient failed to achieve metabolic control for unknown reasons. Despite the small number of patients in our study, the use of Bayesian analysis allows to determine the metabolic efficacy of the combined islet-lung transplantation.

Our study also showed the benefit of combined islet-lung transplantation for quality of life. A marked improvement was observed in physical parameters, as it has previously been reported in CF patients after lung transplantation.<sup>31</sup> Psychological parameters did not significantly change and were already scored highly prior to transplantation, most likely due to the patients' positive perception of the upcoming procedure. Diabetes-related quality of life was only modestly improved, in contrast to observations in type 1 diabetes patients following islet transplantation,<sup>32</sup> indicating that the majority of the quality of life improvements in our study are related to the effects of lung transplantation.

In terms of safety, we found the safety profile of combined islet-lung transplantation to be similar to that of lung transplantation alone. Lung infection is the most common complication of lung transplantation, and we found this to also be the case with the combined lung-islet procedure. Rates of lung infection were similar to those observed in a series of lung transplant patients<sup>33</sup> and all SAEs resolved without sequelae. The supplementary islet perfusion procedure does not, therefore, appear to increase morbidity associated with lung transplantation. Although we observed no mortality, the pilot nature of this study and the small number of participants involved mean that larger scale studies are required to meaningfully assess mortality rates.

The minimally invasive percutaneous approach for islet infusion offers several advantages in the early postoperative period of lung transplantation. The procedure-related morbidity of intraportal islet infusion is low compared to that of pancreas transplantation.<sup>34</sup> Lung-pancreas transplantation is technically more complex, carrying a higher risk of complications due to the simultaneous thoracic



**FIGURE 3** Respiratory function parameters. FEV1 expressed in (A) liters and (B) percentages and FVC expressed in (C) liters and (D) percentages at baseline and at 3 (3 M), 6 (6 M), and 12 (12 M) months after combined lung-islet transplantation. The error bars indicate the ranges. FEV1, forced expiratory volume expired in 1 s; FVC, forced vital capacity. Results are expressed as boxplots with median, minimum, maximum values and IQR

and abdominal procedures in already very weak patients. However, whole organ pancreas transplantation offers the possibility of optimized glycemic control, complete insulin independence, and the correction of pancreatic exocrine insufficiency, which is extremely common in this population. An alternative could be to propose pancreas transplantation following recovery from lung transplantation.<sup>35</sup> In the case of lung-islet transplantation, islet cells can be successfully maintained in culture for up to 10 days, allowing implantation to be delayed until the patient's clinical condition has improved. Although a small risk of serious complications is associated with this procedure in type 1 diabetes patients,<sup>36</sup> we observed no complications related to islet injection in our study. This difference may be explained by the specific diabetes-related coagulation state of type 1 diabetes patients, which is not found in CF patients.

The use of the same single donor for lung and islet transplantation may also offer immunological advantages, by reducing immunogenicity, and therefore reducing the risk of rejection. Indeed, we observed a lower rate of lung rejection, with only two cases of acute lung graft rejection requiring steroid bolus, compared to the 40% which has been reported after lung transplantation alone.<sup>37</sup> The immunosuppression protocol was designed to allow control of pulmonary rejection and to reduce damage to the transplanted islets. Contrary to islet transplantation in patients with type 1 diabetes, we did not use etanercept in our study. However, the target doses of tacrolimus were a compromise between the low doses used in the standard Edmonton protocol and the doses used in lung transplantation.

Indeed, this difference in immunosuppression regime may have impacted our results, although it is difficult to speculate on the exact nature and magnitude of such a potential impact.

The use of a single donor, however, limits the quantity of islets that can be isolated. In our study, the weak increase in C-peptide and the modest reduction in posttransplant insulin requirements can be explained by the low number of transplanted islets isolated from a single donor pancreas, despite the residual insulin secretion which occurs in CFRD. For patients with type 1 diabetes, at least 10,000 IEQ/kg from two or three pancreas donors are necessary to ensure insulin independence. An alternative approach would be to delay islet transplantation and provide the islet graft from several different donors, as has been successfully carried out in both type 1 diabetes and CF patients.<sup>38,39</sup>

Combined lung-islet transplantation is a relatively new therapeutic option for CF patients, and the best candidates for this treatment remain to be defined. In a retrospective study, Valour et al showed that 60% of patients with uncontrolled CFRD (HbA1c >7%, insulin dose >1 IU/kg/day) prior to lung transplantation gained metabolic control after the graft and suggested that combined islet-lung transplantation may most benefit patients whose diabetes is linked to decreased insulin secretion.<sup>14</sup> The results of our study, whose inclusion criteria encompass a subgroup of patients with end-stage CF, uncontrolled CFRD, and impaired pancreatic insulin secretion, reinforce the suggestion that the combined procedure is of benefit within this specific population.

**TABLE 2** Number of serious and non-serious adverse events during the 1 year of follow-up after islet-lung transplantation

	0–1 month	1–12 months	Total
Number of AEs	133	164	296
Number of non-serious AEs	97	132	229
Number of SAEs	36	28	67
Infections and infestations (n)	9	9	18
Respiratory, thoracic, and mediastinal disorders (n)	8	4	12
Vascular disorders (n)	9	0	9
Gastrointestinal disorders (n)	1	4	5
Immune system disorders (n)	1	3	4
Renal and urinary disorders (n)	2	2	4
Cardiac disorders (n)	3	0	3
Metabolism and nutrition disorders (n)	1	2	3
Blood and lymphatic system disorders (n)	1	1	2
Injury, poisoning, and procedural complications (n)	2	0	2
General disorders and administration site conditions (n)	0	1	1
Musculoskeletal and connective tissue disorders (n)	0	1	1
Nervous system disorders (n)	1	0	1
Product (device) issues (n)	0	1	1
Psychiatric disorders (n)	1	0	1

Note: Different classes of SAEs and numbers reported for each class are detailed.

Abbreviations: AEs, adverse events; SAEs, serious adverse events.

The main limitation of our study is the absence of control group. Improvements in outcome measures such as weight increase, BMI, respiratory parameters, and quality of life are to be expected following lung transplantation and therefore cannot be solely attributed to the combined islet procedure. However, this trial is the first to be carried out in islet-lung transplantation using a standardized protocol across several centers and provides valuable data. To prove the real benefit of combined islet-lung transplantation for CF patients, it would be interesting to carry out a comparative, randomized trial evaluating the metabolic evolution of patients who received combined islet-lung transplantation versus lung transplantation and insulin therapy. The use of repeated islet infusion from several donors should also be explored. However, this type of study is highly challenging, owing to the rarity of CF and difficulties in recruiting sufficient numbers of eligible participants. An alternative, more feasible approach would be to carry out an international, multicentric trial, employing the present standardized protocol. This would allow to significantly increase the amount of data collected on the efficacy of combined lung-islet transplantation within this particular population.

A second limitation is that the new composite score employed in this study has not yet been validated. For type 1 diabetes patients,

islet transplantation has been developed without a clear definition of the functional and clinical outcomes which define graft success. Given that insulin independence or C-peptide levels alone are not good markers for metabolic efficacy, the use of composite markers, such as the Beta, Beta 2, IglS scores, which take into account C-peptide, HbA1c, fasting glycemia, insulin needs, and hypoglycemia parameters, have been proposed as better alternatives.<sup>40</sup> However, these scores cannot be applied to CFRD patients, due to the presence of persistent endogenous insulin secretion with detectable C-peptide, the low reliability of HbA1c in CF patients, and the low number of hypoglycemic events linked to residual insulin secretion. As no definitive score of metabolic control has been validated for CFRD, we applied a modified version of the existing beta score, tailored to CFRD by removing the C-peptide component and replacing this with weight, an important metabolic marker for CF patients. Further work on the validation of such scores is merited and would be of use in future clinical studies. Recently, the IglS 2.0 score, based on HbA1c values and CGM data, has been proposed.<sup>40</sup> Applied to our six patients with CGM data, combined islet-lung transplantation was a success in five out of six patients versus four out of six with our composite score. Due to the limited availability of CGM at the start of this study, we were unable to use these criteria as a primary end point.

The results of this study indicate that combined islet-lung transplantation is an efficient and viable therapeutic option for patients with end-stage CF and CFRD, whose numbers are on the rise due to the increased life expectancy of CF patients. It should be noted, however, that the absence of a lung transplantation alone control group in our study means that the results of combined lung islet transplantation cannot be attributed to the islet transplantation alone. While larger studies will be challenging, they will be of utmost importance in defining the long-term benefits of this treatment and identifying the best-suited candidates, in turn, allowing to optimize clinical outcomes.

## ACKNOWLEDGMENTS

The authors are indebted to clinical research nurses and the staff of the Department of Endocrinology, Diabetology, and Nutrition and Direction de la Recherche Clinique et de l'Innovation of Strasbourg University Hospital, the team of Biostatistics and Data management, Hospice Civil, Lyon, France, the GRAGIL (Groupe Rhin Rhône Alpes Genève pour la greffe d'îlots pancréatique) Swiss-French network, and the national TREPID group (groupe d'étude de la TRansplantation de Pancreas et d'Ilots pancréatiques pour le Diabète). Manuscript edition was provided by Dr. Kate Dunning (University Hospital of Strasbourg). This study was supported by the French Ministry of Health, Programme Hospitalier de Recherche Clinique 2011, the French patient association VLM (Vaincre La Mucoviscidose).

## DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.


**PRIOR PRESENTATION**

Partial results were previously published in abstract form and presented as a poster or oral communication at the 10th International Congress on Lung Transplantation, September 7, 2016, Paris, France, at 38th Artificial Insulin Delivery Systems, Pancreas and Islet Transplantation (AIDPIT) Workshop, Innsbruck, Austria, January 27–29, 2017, and at 41st European Cystic Fibrosis Conference, Belgrade, Serbia, June 8, 2018.

**DATA AVAILABILITY STATEMENT**

The study protocol and statistical analysis plan are available upon request.

**ORCID**

Benjamin Renaud Picard  <https://orcid.org/0000-0003-3492-9486>

Thierry Berney  <https://orcid.org/0000-0002-4230-9378>

Romain Kessler  <https://orcid.org/0000-0002-5798-5715>

Laurence Kessler  <https://orcid.org/0000-0002-1769-5625>

**REFERENCES**

1. Hadjiliadis D. Special considerations for patients with cystic fibrosis undergoing lung transplantation. *Chest*. 2007;131(4):1224-1231. doi:10.1378/chest.06-1163
2. Khush KK, Cherikh WS, Chambers DC, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult heart transplantation report - 2019; focus theme: donor and recipient size match. *J Heart Lung Transplant*. 2019;38(10):1056-1066. doi:10.1016/j.healun.2019.08.004
3. Stephenson AL, Sykes J, Stanojevic S, et al. Survival comparison of patients with cystic fibrosis in Canada and the United States: a population-based cohort study. *Ann Intern Med*. 2017;166(8):537-546. doi:10.7326/M16-0858
4. Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. *Diabetes Care*. 2009;32(9):1626-1631. doi:10.2337/dc09-0586
5. Chamnan P, Shine BSF, Haworth CS, Bilton D, Adler AI. Diabetes as a determinant of mortality in cystic fibrosis. *Diabetes Care*. 2010;33(2):311-316. doi:10.2337/dc09-1215
6. Lavie M, Fisher D, Vilozni D, et al. Glucose intolerance in cystic fibrosis as a determinant of pulmonary function and clinical status. *Diabetes Res Clin Pract*. 2015;110(3):276-284. doi:10.1016/j.diabetes.2015.10.007
7. Kerem E, Viviani L, Zolin A, et al. Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS patient registry. *Eur Respir J*. 2014;43(1):125-133. doi:10.1183/09031936.00166412
8. Brennan AL, Geddes DM, Gyi KM, Baker EH. Clinical importance of cystic fibrosis-related diabetes. *J Cyst Fibros*. 2004;3(4):209-222. doi:10.1016/j.jcf.2004.08.001
9. Hackman KL, Bailey MJ, Snell GI, Bach LA. Diabetes is a major risk factor for mortality after lung transplantation. *Am J Transplant*. 2014;14(2):438-445. doi:10.1111/ajt.12561
10. Hofer M, Schmid C, Benden C, et al. Diabetes mellitus and survival in cystic fibrosis patients after lung transplantation. *J Cyst Fibros*. 2012;11(2):131-136. doi:10.1016/j.jcf.2011.10.005
11. Mainbourg S, Philit F, Touzet S, et al. Cystic fibrosis-related diabetes before lung transplantation is associated with lower survival but does not affect long-term renal function. *Pediatr Pulmonol*. 2019;54(7):977-983. doi:10.1002/ppul.24307

12. Bradbury RA, Shirkhedkar D, Glanville AR, Campbell LV. Prior diabetes mellitus is associated with increased morbidity in cystic fibrosis patients undergoing bilateral lung transplantation: an "orphan" area? A retrospective case-control study. *Intern Med J*. 2009;39(6):384-388. doi:10.1111/j.1445-5994.2008.01786.x
13. Hadjiliadis D, Madill J, Chaparro C, et al. Incidence and prevalence of diabetes mellitus in patients with cystic fibrosis undergoing lung transplantation before and after lung transplantation. *Clin Transplant*. 2005;19(6):773-778. doi:10.1111/j.1399-0012.2005.00420.x
14. Valour F, Brault C, Abbas-Chorfa F, et al. Outcome of cystic fibrosis-related diabetes two years after lung transplantation. *Respiration*. 2013;86(1):32-38. doi:10.1159/000339928
15. Markmann JF, Rickels MR, Eggerman TL, et al. Phase 3 trial of human islet-after-kidney transplantation in type 1 diabetes. *Am J Transplant*. 2021;21(4):1477-1492. doi:10.1111/ajt.16174
16. Hering BJ, Clarke WR, Bridges ND, et al. Phase 3 trial of transplantation of human islets in type 1 diabetes complicated by severe hypoglycemia. *Diabetes Care*. 2016;39(7):1230-1240. doi:10.2337/dc15-1988
17. Lablanche S, Vantigham M-C, Kessler L, et al. Islet transplantation versus insulin therapy in patients with type 1 diabetes with severe hypoglycaemia or poorly controlled glycaemia after kidney transplantation (TRIMECO): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2018;6(7):527-537. doi:10.1016/S2213-8587(18)30078-0
18. Vantigham M-C, Chetboun M, Gmyr V, et al. Ten-year outcome of islet alone or islet after kidney transplantation in type 1 diabetes: a prospective parallel-arm cohort study. *Diabetes Care*. 2019;42(11):2042-2049. doi:10.2337/dc19-0401
19. Tschopp J-M, Brutsche MH, Frey J-G, et al. End-stage cystic fibrosis: improved diabetes control 2 years after successful isolated pancreatic cell and double-lung transplantation. *Chest*. 1997;112(6):1685-1687. doi:10.1378/chest.112.6.1685
20. Kessler L, Bakopoulou S, Kessler R, et al. Combined pancreatic islet-lung transplantation: a novel approach to the treatment of end-stage cystic fibrosis. *Am J Transplant*. 2010;10(7):1707-1712. doi:10.1111/j.1600-6143.2010.03143.x
21. Wojtusciszyn A, Branchereau J, Esposito L, et al. Indications for islet or pancreatic transplantation: Statement of the TREPID working group on behalf of the Société francophone du diabète (SFD), Société française d'endocrinologie (SFE), Société francophone de transplantation (SFT) and Société française de néphrologie - dialyse - transplantation (SFNDT). *Diabetes Metab*. 2019;45(3):224-237. doi:10.1016/j.diabet.2018.07.006
22. Copeland H, Copeland J, Hayanga JWA. Cardiac and pulmonary donor procurement. *Curr Opin Organ Transplant*. 2018;23(3):281-285. doi:10.1097/MOT.0000000000000530
23. Yun JJ, Unai S, Pettersson G. Lung transplant with bronchial arterial revascularization: review of surgical technique and clinical outcomes. *J Thorac Dis*. 2019;11(Suppl 14):S1821-S1828. doi:10.21037/jtd.2019.09.09
24. Bucher P, Mathe Z, Morel P, et al. Assessment of a novel two-component enzyme preparation for human islet isolation and transplantation. *Transplantation*. 2005;79(1):91-97. doi:10.1097/01.tp.0000147344.73915.c8
25. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ*. 1992;305(6846):160-164. doi:10.1136/bmj.305.6846.160
26. Jacobson AM, de Groot M, Samson JA. The evaluation of two measures of quality of life in patients with type I and type II diabetes. *Diabetes Care*. 1994;17(4):267-274. doi:10.2337/diacare.17.4.267
27. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest*. 2005;128(4):2347-2354. doi:10.1378/chest.128.4.2347

28. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf*. 1999;20(2):109-117. doi:[10.2165/00002018-199920020-00002](https://doi.org/10.2165/00002018-199920020-00002)
29. Thall PF, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Stat Med*. 1995;14(4):357-379. doi:[10.1002/sim.4780140404](https://doi.org/10.1002/sim.4780140404)
30. Hackman KL, Snell GI, Bach LA. Poor glycemic control is associated with decreased survival in lung transplant recipients. *Transplantation*. 2017;101(9):2200-2206. doi:[10.1097/TP.0000000000001555](https://doi.org/10.1097/TP.0000000000001555)
31. Vermeulen KM, van der Bij W, Erasmus ME, Duiverman EJ, Koëter GH, TenVergert EM. Improved quality of life after lung transplantation in individuals with cystic fibrosis. *Pediatr Pulmonol*. 2004;37(5):419-426. doi:[10.1002/ppul.20009](https://doi.org/10.1002/ppul.20009)
32. Benhamou PY, Milliat-Guittard L, Wojtuszczyzn A, et al. Quality of life after islet transplantation: data from the GRAGIL 1 and 2 trials. *Diabet Med*. 2009;26(6):617-621. doi:[10.1111/j.1464-5491.2009.02731.x](https://doi.org/10.1111/j.1464-5491.2009.02731.x)
33. Bonvillain RW, Valentine VG, Lombard G, LaPlace S, Dhillon G, Wang G. Post-operative infections in cystic fibrosis and non-cystic fibrosis patients after lung transplantation. *J Heart Lung Transplant*. 2007;26(9):890-897. doi:[10.1016/j.healun.2007.07.002](https://doi.org/10.1016/j.healun.2007.07.002)
34. Perez Daga JA, Perez Rodriguez R, Santoyo J. Immediate post-operative complications (I): post-operative bleeding; vascular origin: Thrombosis pancreatitis. *World J Transplant*. 2020;10(12):415-421. doi:[10.5500/wjt.v10.i12.415](https://doi.org/10.5500/wjt.v10.i12.415)
35. Fridell JA, Lutz AJ, Powelson JA. Simultaneous pancreas and kidney transplant after bilateral lung transplant for a recipient with cystic fibrosis. *Am J Transplant*. 2021;21(9):3180-3183. doi:[10.1111/ajt.16597](https://doi.org/10.1111/ajt.16597)
36. CITR Research Group. 2007 update on allogeneic islet transplantation from the Collaborative Islet Transplant Registry (CITR). *Cell Transplant*. 2009;18(7):753-767. doi:[10.3727/096368909X470874](https://doi.org/10.3727/096368909X470874)
37. Snell G, Reed A, Stern M, Hadjiliadis D. The evolution of lung transplantation for cystic fibrosis: a 2017 update. *J Cyst Fibros*. 2017;16(5):553-564. doi:[10.1016/j.jcf.2017.06.008](https://doi.org/10.1016/j.jcf.2017.06.008)
38. Spijker HS, Wolffenbuttel BHR, van der Bij W, Engelse MA, Rabelink TJ, de Koning EJP. Islet-after-lung transplantation in a patient with cystic fibrosis-related diabetes. *Diabetes Care*. 2014;37(7):e159-e160. doi:[10.2337/dc14-0639](https://doi.org/10.2337/dc14-0639)
39. Klee P, Dirlewanger M, Lavallard V, et al. Combined pancreatic islet-lung-liver transplantation in a pediatric patient with cystic fibrosis-related diabetes. *Horm Res Paediatr*. 2018;90(4):270-274. doi:[10.1159/000488107](https://doi.org/10.1159/000488107)
40. Landstra CP, Andres A, Chetboun M, et al. Examination of the IglS criteria for defining functional outcomes of  $\beta$ -cell replacement therapy: IPITA symposium report. *J Clin Endocrinol Metab*. 2021;106(10):3049-3059. doi:[10.1210/clinem/dgab386](https://doi.org/10.1210/clinem/dgab386)

## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Rakotoarisoa L, Wagner C, Munch M, et al. Feasibility and efficacy of combined pancreatic islet-lung transplantation in cystic fibrosis-related diabetes-PIM study: A multicenter phase 1-2 trial. *Am J Transplant*. 2022;22:1861-1872. doi:[10.1111/ajt.17058](https://doi.org/10.1111/ajt.17058)