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A Randomized Trial Comparing Imlifidase to Plasmapheresis in Kidney Transplant Recipients With Antibody-Mediated Rejection

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ABSTRACT

Background: Antibody-mediated rejection (ABMR) poses a barrier to long-term graft survival and is one of the most challenging events after kidney transplantation. Removing donor specific antibodies (DSA) through therapeutic plasma exchange (PLEX) is a cornerstone of antibody depletion but has inconsistent effects. Imlifidase is a treatment currently utilized for desensitization with near-complete inactivation of DSA both in the intra- and extravascular space.

Methods: This was a 6-month, randomized, open-label, multicenter, multinational trial conducted at 14 transplant centers. Thirty patients were randomized to either imlifidase or PLEX treatment. The primary endpoint was reduction in DSA level during the 5 days following the start of treatment.

Results: Despite considerable heterogeneity in the trial population, DSA reduction as defined by the primary endpoint was 97% for imlifidase compared to 42% for PLEX. Additionally, imlifidase reduced DSA to noncomplement fixing levels, whereas PLEX failed to do so. After antibody rebound in the imlifidase arm (circa days 6–12), both arms had similar reductions in DSA. Five allograft losses occurred during the 6 months following the start of ABMR treatment—four within the imlifidase arm (18 patients treated) and one in the PLEX arm (10 patients treated). In terms of clinical efficacy, the Kaplan–Meier estimated graft survival was

Abbreviations: ABMR, antibody-mediated rejection; ADA, antidrug antibodies; ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; DSA, donor-specific antibodies; DSA_0, DSA at predose; DSA_t, sum of DSA at nadir up to and including 5 days after treatment; eGFR, estimated glomerular filtration rate; IA, immunoadsorption; IFTA, interstitial fibrosis and tubular atrophy; i-IFTA, inflammation of the IFTA; IVIg, intravenous immune globulin; MFI, mean fluorescent intensity; MMDx, molecular microscope diagnostic system; PD, pharmacodynamic analysis; PLEX, plasma exchange; SAB, single-antigen bead assay; scIgG, single cleaved IgG; TCMR, T-cell–mediated rejection.

78% for imlifidase and 89% for PLEX, with a slightly higher eGFR in the PLEX arm at the end of the trial. The observed adverse events in the trial were as expected, and there were no apparent differences between the arms.
Conclusion: Imlifidase was safe and well-tolerated in the ABMR population. Despite meeting the primary endpoint of maximum DSA reduction compared to PLEX, the trial was unsuccessful in demonstrating a clinical benefit of imlifidase in this heterogenous ABMR population.
Trial Registration: EudraCT number: 2018-000022-66, 2020-004777-49; ClinicalTrials.gov identifier: NCT03897205, NCT04711850

1 | Background

Kidney transplantation remains the preferred treatment modality for end-stage kidney disease given its morbidity and mortality benefits compared to dialysis. However, antibody-mediated rejection (ABMR) poses a barrier to long-term graft survival and is one of the most challenging events after kidney transplantation. Despite advances in understanding the underlying pathophysiological processes, ABMR remains one of the main causes leading to allograft failure [1]. In ABMR, donor-specific antibodies (DSAs) interact with the kidney endothelium, which then activates cellular and complement-mediated pathways responsible for the development of microcirculatory changes and forthcoming tissue injury. ABMR can occur in patients with pre-existing DSA at the time of transplantation or in patients without DSA at transplantation who develop de novo DSA over time.

The gold standard method of diagnosing ABMR is kidney transplant biopsy, which is an invasive method associated with some risk. Biopsies may be delayed (both in obtaining one and in the pathological readout) and detect damage that has already occurred, which may render available treatments less effective [2]. Currently, there are no approved therapies for the treatment of ABMR and standard of care varies by center and most commonly consists of any combination of steroid pulses, therapeutic plasma exchange (PLEX), immunoadsorption (IA), intravenous immune globulin (IVIg), complement inhibition, proteosome inhibition, IL-6 targeted therapies, and/or anti-CD20 monoclonal antibodies. These therapies have variable effects and may take weeks before DSA levels are sufficiently reduced; in some cases the treatments are ineffective in reducing DSAS.

A major barrier in the advancement of understanding the optimal treatment of ABMR is the heterogeneity in the diagnosis with serological, clinical, and morphologic/molecular presentation, including inactive, active, mixed, and chronic rejections. This has been observed in clinical studies, especially as it pertains to patient characterization, DSA characterization, and clinical endpoint definition. Patients are often treated with combination therapies, which makes analysis of efficacy of any one agent difficult. Studies comparing ABMR treatments are also limited due to the use of differing ABMR definitions and immunologic and histologic parameters.

Imlifidase is an IgG-degrading enzyme originating from *Streptococcus pyogenes*, which cleaves all four human subclasses of IgG with strict specificity. Imlifidase hydrolyzes the IgG molecule below the hinge region and thereby generates one $F(ab)'_2$ fragment and one Fc fragment. These fragments neither bind to Fcγ receptors nor activate the complement system. Thus, the proteolytic activity of imlifidase on IgG molecules prevents IgG-mediated phagocytosis, antibody-dependent cellular cytotoxicity, and complement-mediated injury [3–7]. The speed of the reaction is a major advantage, and it remains the only therapy, to date, with near-complete inactivation of DSA both in the intra- and extravascular space. Within a few hours of dosing, the entire pool of IgG is fully cleaved, thereby creating essentially an IgG-free window of approximately 1 week [8, 9]. Imlifidase has also been used successfully in a single case of treating refractory liver ABMR, where other treatments failed to deplete the antibody burden [10].

In this study we demonstrate the superiority of imlifidase to rapidly diminish DSA in comparison with PLEX in a randomized clinical trial of kidney transplant recipients with ABMR.

2 | Methods

This was a randomized, open-label, multicenter, multinational trial conducted at 14 transplant centers in five countries: Germany (Charité-Universitätsmedizin, Berlin; Medizinische Hochschule, Hannover), Austria (Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna), France (Hôpital Pellegrin, CHU Bordeaux, Bordeaux; CHU Grenoble Alpes, Grenoble; Hôpital Saint-Louis, Paris; Hôpital Necker, Paris), United States (Cedars-Sinai Medical Center, Los Angeles, CA; New York University Langone Health, New York, NY; Mayo Clinic Hospital, Rochester, MN; Brigham and Women's Hospital, Boston, MA), and Australia (Royal Adelaide Hospital, Adelaide; The Royal Melbourne Hospital, Melbourne; Royal Prince Alfred Hospital, Sydney) between April 30, 2019, and November 11, 2022.. Additionally, graft and patient survival data up to Day 180 in the long-term follow-up trial (20-HMedIdeS-18) was used. The trials were conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki; all ethical and regulatory approvals were available before any patient was exposed to any trial-related procedure. Thirty patients were randomized to either imlifidase or PLEX treatment in a 2:1 ratio according to computer-generated randomization. The primary objective of the trial was to confirm the well-established properties of imlifidase within desensitization prior to kidney transplantation [8, 9] for the ABMR indication and additionally compare to an active control group consisting of plasmapheresis.

2.1 | Eligibility

Adult patients, ≥18 years of age, with a kidney transplant with presence of DSA(s) who met Banff 2017 criteria for active or

chronic active ABMR were eligible for inclusion. Clinical parameters included at least a 25% rise in serum creatinine compared to the last individual value taken prior to ABMR diagnosis. Patients with delayed graft function and ABMR within 10 days of transplantation were eligible for inclusion regardless of serum creatinine level. The full list of inclusion/exclusion criteria is available in Table S1.

2.2 | Donor-Specific Antibody Assessment

In addition to the locally analyzed DSA used for inclusion, DSA was analyzed centrally for assessment of the endpoints (Hansa Biopharma AB, Lund, Sweden) measured using single-antigen bead assay (SAB, LABScreen, One Lambda, ThermoFisher Scientific, West Hills, CA). Serum samples were pretreated with EDTA and DSA was defined as any HLA mismatch with a mean fluorescent intensity (MFI) of more than 1000. In addition, DSA was analyzed for complement fixation using C1q (C1qScreen, One Lambda, ThermoFisher Scientific, West Hills, CA) and cut-off for complement fixation was set to 10 000 MFI. Individual DSA was determined at the allele level if only antigen HLA mismatches were available using the highest allele matching that antigen.

2.3 | Clinical Evaluation

Renal function was assessed throughout the trial by serum creatinine and estimated glomerular filtration rate (eGFR) according to the abbreviated modification of diet in renal disease formula. Urine albumin/creatinine ratio was analyzed continuously throughout the trial period. ABMR was diagnosed according to Banff 2017 or 2019 criteria by respective institution's pathologist. In all, three kidney biopsies were collected: at screening and at trial Day 29 and Day 180; all were evaluated with histopathology and whenever possible with microarray mRNA measurement (Molecular Microscope Diagnostic System (MMDx), Transcriptome, Alberta, Canada). Banff diagnostic categories based on locally generated scores and MMDx scores were corroborated centrally in accordance with Banff guidelines. Allograft loss was defined as the first date of continuing dialysis.

2.4 | ABMR Treatment

The treatment schedules for the two treatment arms are depicted in Figure 1. Imlifidase at 0.25 mg/kg body weight was administered as a single intravenous infusion over 15 min. PLEX was administered as 5–10 sessions as judged necessary by the investigator. All patients received pulse methylprednisolone 500 mg IV for 3 days, which started before the first treatment and was followed by a tapering schedule with either oral prednisolone or oral prednisone. The patients treated with imlifidase also received antihistamines before treatment. In addition, high-dose IVIg 10% solution 2 g/kg body weight (maximum dose 140 g) was administered 3 days after imlifidase treatment or directly after the last PLEX session. IVIg was generally administered over 2 days. Thereafter, a single dose of rituximab (anti-CD20) 375 mg/m^2 IV was given 5 days after IVIg infusion in both arms was complete. Other treatments and/or procedures for the treatment of ABMR could be used at any timepoint as needed if trial treatments were deemed ineffective, per the discretion of the investigator. Maintenance immunosuppression was administered according to standard clinical practice for ABMR patients at each trial center.

2.5 | Trial Endpoints

The primary endpoint was the maximum reduction in DSA level at any timepoint during the 5 days following the start of treatment and calculated for each patient as the reduction (%) in sum of DSAs: $100 \times (DSA_0 - DSA_t)/DSA_0$, where DSA_0 = DSA at predose and DSA_t = the sum of DSA nadir up to and including 5 days after treatment. Secondary endpoints were DSA levels (including C1q complement-fixing DSA), kidney function, graft survival, histopathology of biopsies including mRNA levels, number of PLEX sessions needed, pharmacokinetics, pharmacodynamics, safety, tolerability, and the immunogenicity profile of imlifidase assessed as development of antidrug antibodies.

2.6 | Statistical Analysis

Descriptive statistics were used to summarize the patient characteristics and trial endpoints. For the primary endpoint, the difference in reduction between the two treatments was presented with a 95% confidence interval. The confidence interval for the difference in the reduction was found by using an analysis of variance model with treatment as fixed effect, as specified in the trial's statistical analysis plan. The continuous efficacy endpoints are presented by counts and percentages. The safety endpoints are summarized as for the efficacy endpoints. No formal statistical hypothesis testing was performed. In general, missing data were not imputed or adjusted in other ways. Median value is presented with minimum and maximum values. No sample size calculation was performed for this trial. Statistical significance was determined with a p value below 0.05 using Mann–Whitney U test.

3 | Results

3.1 | Demographic and ABMR Baseline Characteristics

Thirty patients were randomized, with 29 patients treated. One patient was incorrectly randomized (to the imlifidase arm) but not treated because the DSA inclusion criteria were not met. In addition, one of the treated (randomized to imlifidase) patients also failed the DSA inclusion criteria and was therefore not included in the efficacy analysis. The patients were predominantly Caucasian (82%), recipients of deceased donors (79%), and with a large time span since transplantation, ranging from 8 days to 26 years, at the time of trial treatment (Table 1). Eight (29%) patients had received desensitization prior to the current transplantation and 5 (18%) patients had a history of previous ABMR.

The ABMR baseline characteristics were very heterogeneous (Table 1). The screening biopsies showed that only 9 (32%) patients had solely active ABMR with the remaining presenting with a combination of chronic active ABMR or mixed rejection.

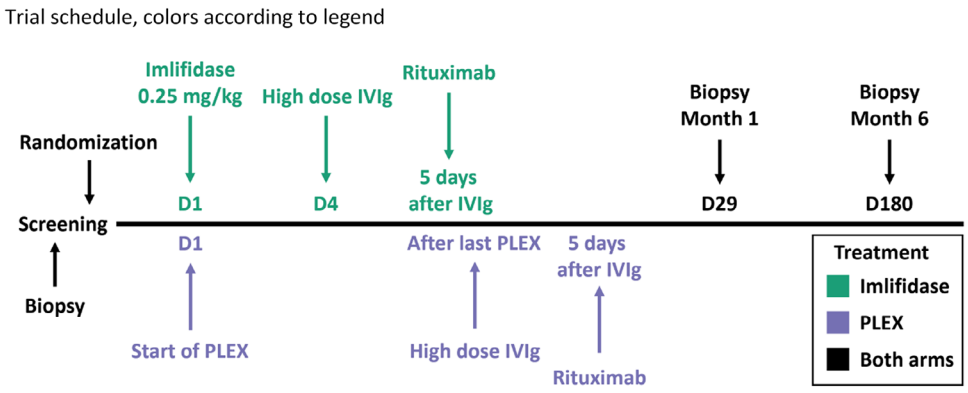

FIGURE 1 | Trial schedule (colors according to legend).

TABLE 1 | Demography and baseline ABMR characteristics.

	Imlifidase ($n = 18$)	PLEX ($n = 10$)
Age (years), median (range)	43.5 (29–78)	51 (21–78)
Sex, female, *n* (%)	8 (44%)	5 (50%)
Race, *n* (%)		
White	14 (78%)	9 (90%)
Black	4 (22%)	0 (0%)
Asian	0 (0%)	1 (10%)
>1 transplantations, *n* (%)	2 (11%)	2 (20%)
Deceased donor, *n* (%)	15 (83%)	7 (70%)
Time since transplantation (years), median (range)	4 (0.1–25.5)	1.1 (0–13)
Desensitized prior to transplant, *n* (%)	4 (22%)	4 (40%)
Previous ABMR, *n* (%)	4 (22%)	1 (10%)
Pretreatment DSA (sum of MFI), median (range)	11039 (2378–39850)	18922 (530–45053)
Pretreatment DSA (sum of MFI), 1:16 dilution, median (range)	4795 (425–36795)	10228 (167–56915)
Chronic active ABMR, *n* (%)	8 (44%)	5 (50%)
Chronicity score [11], median (range)	5 (1–12), $N = 16$	4 (1–9), $N = 9$
TCMR, *n* (%)	7 (39%)	3 (30%)
Days from biopsy to treatment start, median (range)	5 (2–10)	2.5 (1–8)
Pretreatment eGFR, median (range)	30.2 (0–54.4)	20.2 (10–37.3)

Approximately 50% of the patients had chronic active ABMR at baseline with generally high chronicity scores [11]. There were no significant ($p = 0.72$) differences between the two arms regarding DSA MFI before treatment.

3.2 | DSA Reduction

The median DSA_0 was 11 039 MFI (range: 2378–39 850) and 18 922 MFI (range: 530–45 053) for the imlifidase arm and the PLEX arm, respectively (Table 1), notably the pretreatment DSA was higher, although nonsignificant, for the PLEX arm. DSA reduction is depicted in Figure 2A. The median reduction, as defined by the primary endpoint, was 97% (range: 85%–98%) for imlifidase compared to 42% (range: 5%–82%) for PLEX arm; thus the difference was 51%, with a 95% confidence interval of 37%–66% higher reduction for imlifidase. Two subjects in the PLEX arm were excluded from DSA reduction analysis due to central DSA pretreatment being lower than 1000 MFI. The median time to maximum DSA reduction was 15 h (range 2–72) in the imlifidase arm and 9 days (range 2–180) in the PLEX arm. Both imlifidase and 5–10 rounds of PLEX achieved the same level of DSA reduction after the initial elimination of DSA (Figure 2B).

The DSAs complement fixing ability was assessed by SAB-HLA C1q assay with samples taken pretreatment, at 24 h (Day 2) and at Day 6. Approximately 50% of the patients had complement fixing DSA before treatment (Figure 2C), with no statistical difference

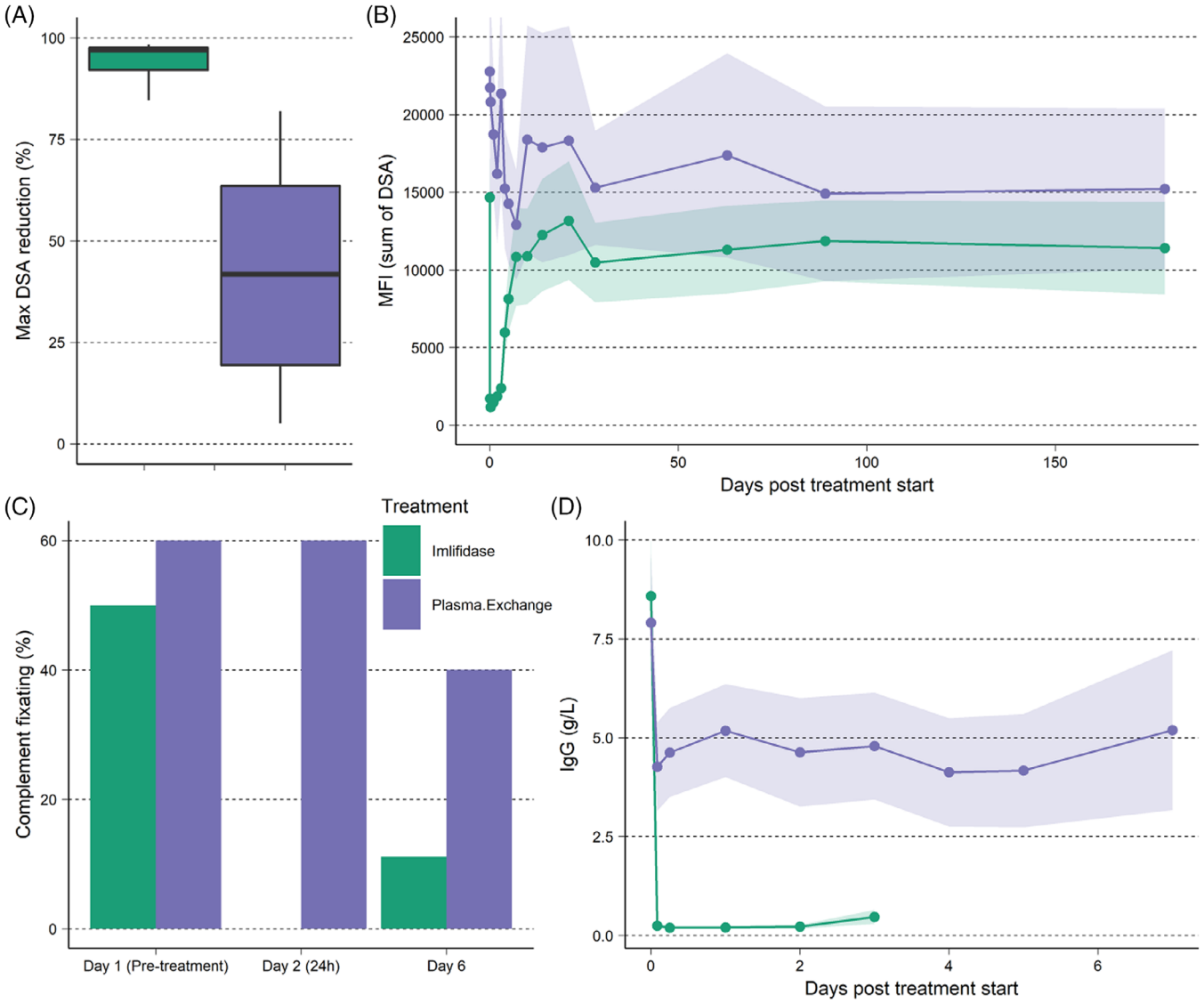

FIGURE 2 | DSA. (A) Reduction within 5 days of start of treatment (primary endpoint); boxplot in the style of Tuckey. (B) DSA up to Day 180 (secondary endpoint); average value with standard error as shaded area. (C) Complement fixation (secondary endpoint); ratio of patients with complement fixing antibodies. (D) Total IgG (secondary endpoint) up to IVIg treatment; average value with standard error as shaded area. Colors according to legend.

between the treatment arms ($p = 0.689$). The complement fixing DSAs were mainly class II HLA-DQ, with 1 patient in the PLEX treatment arm with Class I (HLA-A) antibodies. No complement fixation was detectable 24 h after treatment in any imlifidase-treated patient ($p = 0.0004$), and only 2 of the patients had rebound of C1q fixing antibodies by Day 6 (these 2 patients still had 24% and 76% reduction, respectively, $p = 0.036$). In the PLEX treatment arm, only non-DQ and DP antibodies were reduced to noncomplement fixing levels.

3.3 | Pharmacodynamics

Pharmacodynamic analysis (PD), as measured by total IgG levels (both intact IgG and scIgG), was consistent with previous experience [4, 7] (Figure 2D). Approximately 3% IgG (predominantly scIgG) remained after imlifidase treatment and approximately 50% IgG remained after PLEX treatment (similar to the results seen for DSA (Figure 2B), $p = 0.000007$). The PD measurements (endogenous IgG) are no longer relevant after the initiation of IVIg (exogenous IgG) because exogenous IgG was added to the patient. IVIg treatment was given at 72 h in the imlifidase arm and after the last PLEX session in the PLEX arm. The median day for initiation of IVIg treatment in the PLEX arm was Day 10 (range: 6–15). To avoid confounding the results with the addition of exogenous IVIg, Figure 2D is presented until IVIg was given, which was different for the two treatment arms. Levels of IgG stabilized to pretreatment values by the end of the trial.

3.4 | Number of PLEX Sessions

The number of PLEX sessions for treating the initial ABMR episode in the PLEX arm was 5–10 sessions, with an average of

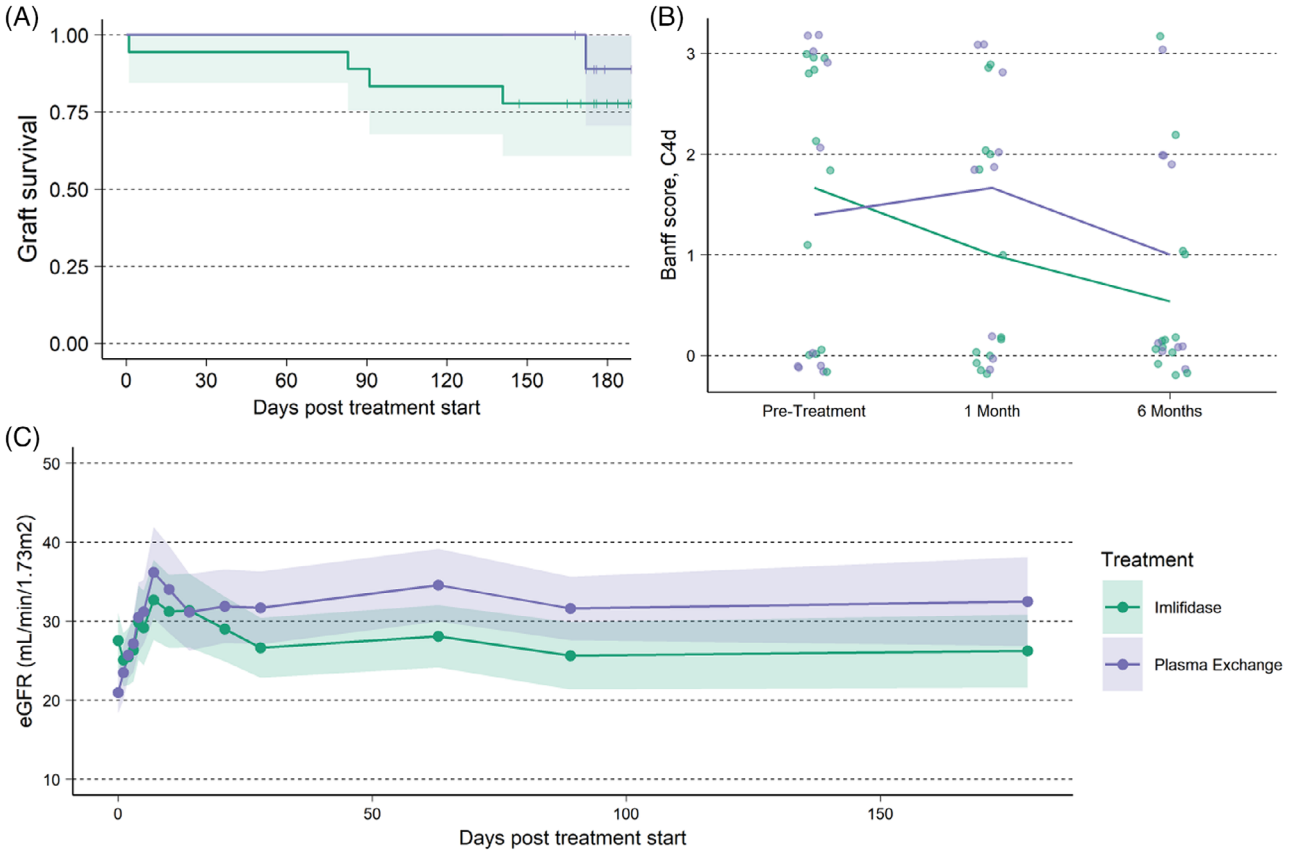

FIGURE 3 | Kidney function. (A) Graft survival (death censored) estimation by Kaplan–Meier; shaded area represents the confidence interval. (B) Biopsy score for C4d; individual values are presented as points and average is presented by line. Only patients with biopsy at 6 months are included ($N = 13$ for imlifidase and $N = 10$ for PLEX). (C) eGFR from treatment up to Day 180; shaded area represents the standard error of the mean. Colors are according to legend.

six sessions. One patient in the imlifidase arm required PLEX for treatment of an acute kidney injury adverse event 2 days after imlifidase treatment, with the event assessed as related to imlifidase treatment due to timing causality. Approximately 20% of the patients in both trial arms required additional PLEX (or immune adsorption) at a later timepoint in the trial to treat reoccurring or persistent high levels of DSA.

3.5 | Kidney Function

Five allograft losses occurred during the 6 months following the start of ABMR treatment—four within the imlifidase arm (18 patients treated) and one in the PLEX arm (10 patients treated). In addition, one subject in the imlifidase arm had started dialysis (i.e., graft loss) prior to trial treatment and was not included in the graft survival analysis. All the allograft losses within the imlifidase arm had concurrent mixed T-cell–mediated rejection (TCMR, $n = 3$) or borderline TCMR ($n = 1$) (Table S2). The Kaplan–Meier estimated graft survival was 78% (CI: 61%–100%) for imlifidase and 89% (CI: 71%–100%) for PLEX (Figure 3A), $p = 0.29$.

At baseline biopsy (Table 1), there were approximately 50% chronic active ABMRs in both treatment arms. At trial end, 3 patients had histological resolution of ABMR and no evidence of rejection. All 3 patients had at pretreatment mixed rejections with a mild ABMR, 1 patient (PLEX arm) had low levels of antibodies (and C4d negative), and 2 patients (one in each arm) had severe TCMR (determined by MMDx). In general, for both arms, no improvement was seen in the biopsy interpretation and most histologic findings stayed the same or worsened.

Histology reading of the biopsies (only including patients with end of trial biopsy) showed that C4d decreased quicker and to a higher extent in the imlifidase arm compared to the PLEX arm (Figure 3B and Table S3) The scores for tubulitis and interstitial inflammation (often linked and associated with TCMR) tended to decrease quicker and more efficiently in the PLEX arm. In addition, the chronic scores of interstitial fibrosis and tubular atrophy (often linked and called IFTA) tended to increase in the imlifidase arm but remained stable in the PLEX arm. The remaining parameters that were collected differed little between the two arms (Table S3). Unfortunately, the scores for assessing chronic active TCMR, i-IFTA, and total inflammation were not collected systematically in the trial, as only occasional cases were reported in the pathologist's description of the biopsy assessment. It should be noted that the scores presented are based on a relatively small number of patients (only subjects with 6-month biopsy; $N = 13$ for imlifidase and $N = 10$ for PLEX) and with significant interpatient variability, timepoints, quality of biopsy specimen, and site-to-site variations.

When MMDx was assessed, there was no difference in multigene scores following imlifidase or PLEX treatments and there was no overall effect of treatment on multigene transcriptomics scores, that is, none of the treatments were effective in changing the gene expression in the kidney.

The eGFR values for the patients are presented in Figure 3C, with patients on dialysis assigned an eGFR of 0 mL/min/m^2. Pretreatment eGFR was somewhat higher in the imlifidase arm, but the variation within both groups was great, without any significant difference (Table 1, $p = 0.208$). The average eGFR increased slightly over the first 7 days and thereafter stabilized at slightly lower from 1 month to the end of the trial. There was an overall average difference of 6 mL/min/1.73 m^2 in eGFR between PLEX and the imlifidase arm ($p = 0.816$) at the end of the trial, largely attributed to the overall allograft losses in the imlifidase arm.

3.6 | Safety

The observed adverse events in the trial were as expected and there were no apparent differences between the arms (Table S4). One death from unknown cause was reported in the imlifidase treatment arm; the death occurred on study Day 176 and was assessed as not related to trial drug.

The level of antidrug antibodies (ADA) measured in this trial was lower, albeit with great interindividual variation, and delayed in relation to treatment in comparison to previous studies with imlifidase [4, 7]. The attenuated and delayed response of ADA was most likely due to the ongoing maintenance immunosuppression, i.e., similar to the attenuated response of vaccine antibodies in kidney transplant recipients [12].

4 | Discussion

To date, imlifidase is the only therapy conditionally approved in Europe and Australia for desensitization in kidney transplantation. As desensitization involves the removal of pathogenic donor-specific antibodies (DSA) prior to transplantation, it is therefore rational to evaluate the same strategy after transplantation for the treatment of antibody-mediated rejection. This is the first trial directly comparing the efficacy and safety of a novel therapy with the current gold standard of plasma exchange for removing DSA in ABMR. Despite publication of recommended consensus ABMR guidelines in 2019, where DSA removal is a cornerstone of treatment with PLEX and IVIg [13], great challenges remain in the treatment of ABMR. In this trial, despite imlifidase demonstrating superiority in both speed and magnitude of reduction of DSA compared with PLEX, this did not translate to a meaningful clinical improvement in the patients during the 6-month follow-up period.

There was great variation in time from transplant, chronicity, cellular involvement, and DSA intensity among the patients enrolled in this pilot trial resulting in a very heterogenous patient population and the trial was not powered to evaluate the clinical treatment effect. This limitation is common with other studies evaluating various treatments of ABMR. For example, upon reanalysis of original data, Marks et al. demonstrated that there was significant difference in treatment effect reported between eculizumab and standard of care in the majority of the patients who had active ABMR but not in the patients whose chronicity of ABMR prevented them to benefit fully from complement inhibition [14]. In the present trial, both chronic active and active ABMR were included. Little clinical effect was seen on chronic active ABMR in either of the cohorts. Data from Haas et al. have shown that patients with active ABMR have better outcomes than those with chronic active ABMR [15]. The authors also showed that better outcomes also were associated with the ability of therapy to durably reduce DSAs. Importantly, they also demonstrated that the presence of significant chronicity features at presentation predicted very poor outcomes. In the present study, it seems that most patients at entry would have fallen into the high-chronicity category as they already had very poor eGFR values at study entry. Additionally, many patients presented with mixed rejections where neither imlifidase nor PLEX would influence the cellular component of the rejection, notwithstanding the fact that all patients received high-dose steroids in the trial. The safety evaluation of the administration of imlifidase to patients diagnosed with ABMR concluded that it was safe and well tolerated and with respect to safety comparable to treatment with PLEX.

Imlifidase's superior removal of antibodies should theoretically translate to a clinical benefit in an antibody-mediated disease such as ABMR, and the lack of clinical efficacy in this trial is most likely associated with a diversity of ABMR phenotypes among the patients selected and/or trial design. If imlifidase is explored in future trials within ABMR, the following factors should be considered: inclusion/exclusion criteria defining maximum time from transplantation, a maximum degree of chronic damage, clear presence of DSA (MFI thresholds and/or C4d positivity), ABMR as primary diagnosis, a minimum eGFR/serum creatinine at inclusion, dialysis independency, lack of concurrent severe TCMR or chronic active TCMR, or inadequate biopsy quality for full Banff diagnosis. Although clinically limiting in recruiting sufficient numbers, these parameters would increase the likelihood of clearly assessing treatment efficacy in a less heterogenous population who may benefit from imlifidase treatment, where rapidly addressing active humoral lesions is most critical.

In this trial, the comparator to imlifidase was PLEX alone, which may not reflect the most current therapeutic strategy and which also includes the use of low dose IVIg (100 mg/kg) between PLEX sessions to prevent DSA rebound. The removal of plasma proteins (in addition to DSA) by PLEX may have uncharacterized benefits in ABMR and/or TCMR and the mechanisms of these combinations are not fully understood.

In conclusion, this trial demonstrated efficacy of DSA reduction comparing imlifidase with PLEX in which imlifidase was clearly successful, especially for complement fixing DSAs. However, the trial was inefficacious in revealing a clinical benefit of imlifidase in this heterogenous population or a significant benefit of either treatment regimen, but this was expected given the small numbers and heterogeneity of the population and the imbalance in the atrophy fibrosis scores. Clinical trials of new agents for the treatment of active or chronic active ABMR must be carefully designed with inclusion criteria that avoid the extremes of chronicity and mixed rejection. Imlifidase may represent only a

single subset in an armamentarium of modalities of this complex immunologic puzzle. Imlifidase is very effective in creating an antibody-free window for a limited time, but the persistence of DSAs and other antibody effector functions such as CDC and ADCC will abrogate this early benefit. To attain longer term gains, a combination of therapeutics that will allow a more durable reduction in DSAs, inhibit CDC and ADCC, and reduce the pathologic and clinical features of antibody-mediated injury is needed to improve patient and graft survival.

Conflicts of Interest

The trial was sponsored by Hansa Biopharma. A.R., P.L., J.T., A.Q.M., and K.S. are employees of Hansa Biopharma. L.C.: Lecture fees: Astellas, Chiesi, Novartis, Sandoz, Ostuka, GSK, Biotest, Hansa. Consultancy fees: Biotest, Hansa Biopharma, Novartis, Otsuka, Takeda, Chiesi. Travel fundings: Astellas, Chiesi, Novartis, Sandoz, Vifor, Otsuka. P.H.: Consultancy fees: Hansa Biopharma.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.