MULTICENTRE, OPEN-LABEL, RANDOMISED, TWO-ARM, SUPERIORITY STUDY ASSESSING BIOAVAILABILITY AND PRACTICABILITY OF ENVARSUS® VERSUS ADVAGRAF® IN LIVER TRANSPLANT RECIPIENTS – ENGRAFT STUDY PROTOCOL

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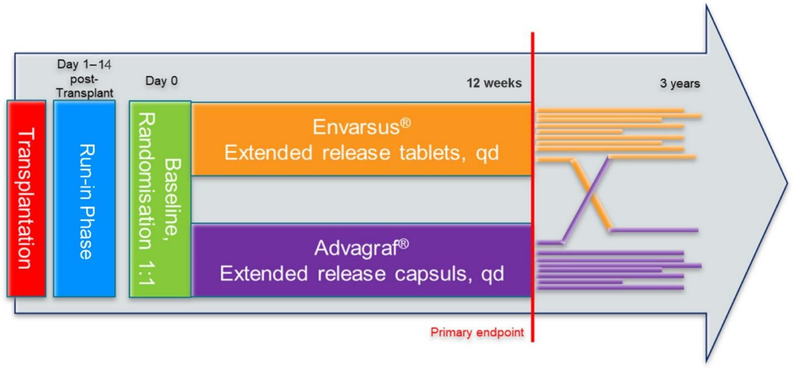
Introduction

Graft rejection and chronic CNI toxicity remain obstacles to organ transplant success. Currently, formulations of tacrolimus such as Prograf® and Advagraf® exhibit limitations in terms of pharmacokinetics and tolerability related in part to suboptimal bioavailability. As dosing non-compliance can result in graft rejection, the once daily formulation of tacrolimus, Advagraf®, was developed (vs 2x/day Prograf®). Benefits of Advagraf® are counterbalanced by delayed achievement of therapeutic trough levels and need for up to 50% higher doses to maintain Prograf®-equivalent troughs. Envarsus® is also a prolonged-release once-daily tacrolimus formulation, developed using MeltDose™ drug-delivery technology to increase drug bioavailability; improved bioavailability results in low patient drug absorption variability and reduced peak-to-trough fluctuations. In phase III de novo kidney transplant studies, Envarsus® proved non-inferior to twice-daily tacrolimus; however, no phase IV studies show superiority of Envarsus® vs Advagraf®.

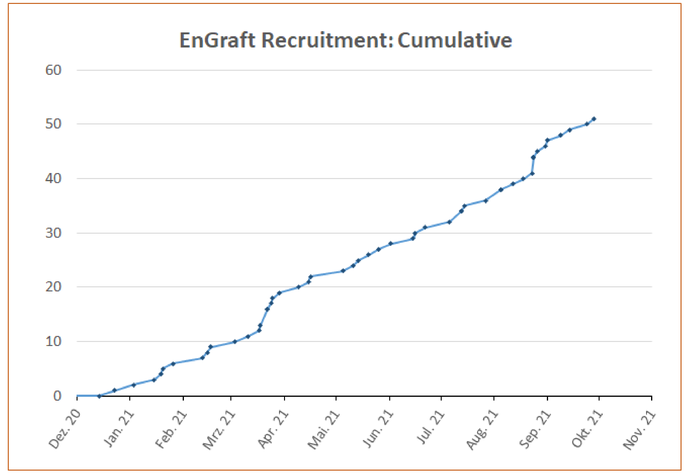
Methods

In EnGraft, we compare bioavailability and test superiority of Envarsus® (test arm) vs Advagraf® (comparator arm) in de novo liver transplant (LTx) recipients. A total of 268 patients from 14 German transplant centres will be randomised 1:1 within 14 days post-LTx. Optional run-in phase in case patients cannot be randomised immediately after transplantation surgery (e.g. unable to swallow IMP) with possible pre-treatment with immediate-release Tacrolimus (e.g. Prograf) or in case of longer delay of CNI introduction. The primary endpoint is dose-normalised trough level (C/D ratio) measured 12 weeks after randomisation. Secondary endpoints include the number of dose adjustments, time to reach first defined trough level and incidence of graft rejections. Additionally, clinical and laboratory parameters will be assessed over a 3 year period.



Conclusion

C/D ratio is an estimate for tacrolimus bioavailability. Improving bioavailability and increasing C/D ratio using Envarsus could reduce renal dysfunction and other tacrolimus-related toxicities; earlier trials have shown that a higher C/D ratio (i.e. slower tacrolimus metabolism) is not only associated with improved renal function, but also linked to reduced neurotoxic side-effects. A higher C/D ratio could improve clinical outcomes for LTx recipients; EnGraft has begun, nearly 20% of patients already recruited.



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