**Supplementary Table 1. Randomised controlled trials of everolimus in combination with CNI in organ transplantation (see text for details)**

| **Study** | **Study phase** | **Patients (n)** | **EVR dose** | **EVR target C0** | **TDM** | **EVR assaya** | **Co-immunosuppression** | **EVR-free comparator arm** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Kidney transplantation** | | | | | | | | |
| Phase II[1](#_ENREF_1) | II | 103 | Fixed dose; 1, 2 or 4 mg/day | N/A | No | ELISA | CsA (standard dose) + GC | None |
| RAD B201[2](#_ENREF_2),[3](#_ENREF_3) | III | 588 | Fixed dose; 1.5 or  3.0 mg/day | N/A | No | LC-MS/MS | CsA (standard dose) + GC | MMF + CsA (standard dose) + GC |
| RAD B251[4](#_ENREF_4) | III | 583 | Fixed dose; 1.5 or  3.0 mg/day | N/A | No | LC-MS/MS | CsA (standard dose) + GC | MMF + CsA (standard dose) + GC |
| A2306[5](#_ENREF_5) | IIIb | 237 | Starting dose 1.5 or  3.0 mg/day | ≥3 ng/mL | Yes | LC-MS/MS | CsA (reduced exposure) + GC | None |
| A2307[5](#_ENREF_5) | IIIb | 256 | Starting dose 1.5 or  3.0 mg/day | ≥3 ng/mL | Yes | LC-MS/MS | Bxmab + CsA (reduced exposure) + GC | None |
| A2309[6](#_ENREF_6) | IIIb | 833 | Starting dose 1.5 or  3.0 mg/day | 3–8 ng/mL or  6–12 ng/mL | Yes | LC-MS/MS | Bxmab + CsA (reduced exposure) + GC | MPA + CsA (standard dose) + GC + Bxmab |
| EVEREST[7](#_ENREF_7) | IIIb | 285 | Starting dose 1.5 mg/day | 3–8 ng/mL or  8–12 ng/mL | Yes | FPIA | CsA (reduced [arm 1] or very-low [arm 2] exposure) + GC + Bxmb | None |
| CRADUS09[8](#_ENREF_8) | III | 92 | Starting dose 1.5 mg/day | ≥3 ng/mL | Yes | LC-MS/MS | Tac (standard [arm 1] or reduced [arm 2] exposure) + GC + Bxmb | None |
| ASSET[9](#_ENREF_9) | III | 228 | Starting dose 3.0 mg/day | 3–8 ng/mL | Yes | LC-MS/MS | Tac (standard [arm 1] or reduced [arm 2] exposure) + GC + Bxmb | None |
| ASCERTAIN[10](#_ENREF_10) | IV | 394 | Starting dose 3.0 mg/day | 3–8 ng/mL | Yes | LC-MS/MS | CsA/Tac (reduced exposure) ± MPA/AZA ± GC | CsA/Tac (standard exposure) ± MPA/AZA ± GC |
| HERAKLES[11](#_ENREF_11) | III | 499 | Starting dose 1.5 mg/day | 3–8 ng/mL | Yes | Local lab | CsA (reduced exposure) + GC + Bxmab | CsA (Standard exposure) + EC-MPS + Bxmab |
| CRAD001AUS92[12](#_ENREF_12) | III | 613 | Starting dose 1.5 mg/day | 3–8 ng/mL | Yes | LC-MS/MS | Tac (reduced exposure) + GC + Bxmb/ATG | MMF + Tac (standard exposure) + GC + Bxmab/ATG |
| CRAD001A2314-CRADLE[13](#_ENREF_13), b | III | 106 planned | 2 mg/m2/dose (not to exceed 0.75 mg/dose) | 3–8 ng/mL | Yes | LC-MS/MS | Tac (reduced exposure) + GC (up to Month 6 post transplant) | MMF + Tac (standard exposure) + GC |
| **Liver transplantation** | | | | | | | | |
| H2304[14](#_ENREF_14) | III | 719 | Starting dose 2.0 mg/day | 3–8 ng/mL | Yes | LC-MS/MS | Tac (reduced exposure) + GC | Tac (standard exposure) + GC |
| **Heart transplantation** | | | | | | | | |
| B253[15](#_ENREF_15) | III | 634 | Fixed dose 1.5 or  3.0 mg/day | N/A | Yes | ELISA | CsA (standard exposure) + GC ± ATG/CD3mab | CsA (standard exposure) + GC + AZA ± ATG/CD3mab |
| A2411[16](#_ENREF_16) | III | 176 | Staring dose 1.5 mg/day | 3–8 ng/mL | Yes | LC-MS/MS | CsA (reduced exposure) + GC ± ATG/IL2Ra | CsA (standard exposure) + MMF + GC ± ATG/IL2Ra |
| A2403[17](#_ENREF_17) | III | 199 | Starting dose 1.5 mg/day | 3–8 ng/mL | Yes | LC-MS/MS | CsA (reduced exposure) + GC ± ATG/IL2Ra | CsA (standard exposure) + GC ± ATG/IL2Ra |
| A2310[18](#_ENREF_18) | III | 721 | Starting dose 1.5 or  3.0 mg/day | 3–8 ng/mL or 6–12 ng/mL | Yes | LC-MS/MS | CsA (reduced exposure) + GC ± Bxmab/ATG | CsA (standard exposure) + MMF + GC ± Bxmab/ATG |
| MANDELA[19](#_ENREF_19) | IV | 200 planned | Centre practice | 5–10 ng/mL | Yes | Local lab | CsA/Tac (reduced exposure) + GC | None (See Supplementary Table 2) |
| **Lung transplantation** | | | | | | | | |
| B159[20](#_ENREF_20) | III | 213 | Starting dose 3.0 mg/day | N/A | No | ELISA | CsA (standard exposure) + GC | AZA + CsA (standard exposure) + GC |
| CeMyLungs[21](#_ENREF_21" \o "Glanville, 2015 #95) | III | 165 | Starting dose 3.0 mg/day | 3–8 ng/mL | Yes | Local lab | CsA (reduced exposure) + GC | CsA (standard exposure) + MPA + GC |
| 4EVERLUNG[22](#_ENREF_22) | III | 232 planned | Centre practice | 4 ± 1 ng/mL | Yes | Local lab | CsA/Tac (reduced exposure) + MPA + GC | CsA/Tac (standard exposure) + MPA + GC |
| **Heart or lung transplantation** | | | | | | | | |
| NOCTET[23](#_ENREF_23) | IV | 282 | 1.5–3.0 mg/day | 3–8 ng/mL | Yes | FPIA | CsA/Tac (reduced exposure) ± MMF ± AZA ± GC | CsA/Tac (standard exposure) ± MMF ± AZA ± GC |

aConducted by central laboratory unless indicated otherwise. bPaediatric study

ASCERTAIN, Assessment of everolimus in addition to CNI reduction in the maintenance of renal transplant recipients; ATG, anti-thymocyte globulin; AZA, azathioprine; Bxmab, basiliximab; CD3mab, muromonab-CD3; CENTRAL, Certican nordic trial in renal transplantation; CsA, ciclosporin A; ELISA, enzyme-linked immunosorbent assay; EVEREST, Everolimus for renal cancer ensuing surgical therapy; EVR, everolimus; FPIA, fluorescence polarization assay; GC, glucocorticoid; IL2Ra, interleukin-2 receptor antagonist; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MMF, mycophenolate mofetil; MPA, mycophenolic acid; N/A not applicable; SCHEDULE, Scandinavian heart transplant everolimus de novo study with early calcineurin inhibitors avoidance; SOCRATES, Steroid or cyclosporin removal after transplant using everolimus; Tac, tacrolimus; TDM, therapeutic drug monitoring.

**References**

1. Kahan BD, Kaplan B, Lorber MI, et al. RAD in de novo renal transplantation: comparison of three doses on the incidence and severity of acute rejection. *Transplantation.* 2001;71:1400–1406.

2. Vitko S, Margreiter R, Weimar W, et al. Everolimus (Certican) 12-month safety and efficacy versus mycophenolate mofetil in de novo renal transplant recipients. *Transplantation.* 2004;78:1532–1540.

3. Vitko S, Margreiter R, Weimar W, et al. Three-year efficacy and safety results from a study of everolimus versus mycophenolate mofetil in de novo renal transplant patients. *Am J Transplant.* 2005;5:2521–2530.

4. Lorber MI, Mulgaonkar S, Butt KM, et al. Everolimus versus mycophenolate mofetil in the prevention of rejection in de novo renal transplant recipients: a 3-year randomized, multicenter, phase III study. *Transplantation.* 2005;80:244–252.

5. Vitko S, Tedesco H, Eris J, et al. Everolimus with optimized cyclosporine dosing in renal transplant recipients: 6-month safety and efficacy results of two randomized studies. *Am J Transplant.* 2004;4:626–635.

6. Tedesco Silva H, Jr., Cibrik D, Johnston T, et al. Everolimus plus reduced-exposure CsA versus mycophenolic acid plus standard-exposure CsA in renal-transplant recipients. *Am J Transplant.* 2010;10:1401–1413.

7. Salvadori M, Scolari MP, Bertoni E, et al. Everolimus with very low-exposure cyclosporine A in de novo kidney transplantation: a multicenter, randomized, controlled trial. *Transplantation.* 2009;88:1194–1202.

8. Chan L, Greenstein S, Hardy MA, et al. Multicenter, randomized study of the use of everolimus with tacrolimus after renal transplantation demonstrates its effectiveness. *Transplantation.* 2008;85:821–826.

9. Langer RM, Hené R, Vitko S, et al. Everolimus plus early tacrolimus minimization: a phase III, randomized, open-label, multicentre trial in renal transplantation. *Transpl Int.* 2012;25:592–602.

10. Holdaas H, Rostaing L, Serón D, et al. Conversion of long-term kidney transplant recipients from calcineurin inhibitor therapy to everolimus: a randomized, multicenter, 24-month study. *Transplantation.* 2011;92:410–418.

11. Budde K, Witzke O, Lehner F, et al. Superior renal function in an everolimus-based calcineurin inhibitor free regimen compared to standard cyclosporine/mycophenolate and low cyclosporine/everolimus: the HERAKLES study [Abstract #50]. *Am J Transplant.* 2012;12(Suppl 3):41.

12. Qazi Y, Shaffer D, Kaplan B, et al. Efficacy and safety of everolimus with low-dose tacrolimus in de novo renal transplant recipients: 12-month randomized study [Abstract #713]. *Am J Transplant.* 2014;14(Suppl 3):80.

13. Ettenger R, Pape L, Tonshoff B, et al. Design and rationale of CRADLE: a randomized, phase III trial evaluating efficacy and safety of early everolimus introduction to reduce CNI exposure and to withdraw steroids in pediatric renal transplant recipients [Abstract #3806.163]. *Presented at the Pediatric Academic Sciences Annual Meeting, May 5th, 2014*. Vancouver, BC, 2014.

14. De Simone P, Nevens F, De Carlis L, et al. Everolimus with reduced tacrolimus improves renal function in de novo liver transplant recipients: a randomized controlled trial. *Am J Transplant.* 2012;12:3008–3020.

15. Eisen HJ, Tuzcu EM, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med.* 2003;349:847–858.

16. Lehmkuhl HB, Arizon J, Vigano M, et al. Everolimus with reduced cyclosporine versus MMF with standard cyclosporine in de novo heart transplant recipients. *Transplantation.* 2009;88:115–122.

17. Zuckermann A, Wang SS, Ross H, et al. Efficacy and safety of low-dose cyclosporine with everolimus and steroids in de novo heart transplant patients: a multicentre, randomized trial. *J Transplant.* 2011;2011:535983.

18. Eisen HJ, Kobashigawa J, Starling RC, et al. Everolimus versus mycophenolate mofetil in heart transplantation: a randomized, multicenter trial. *Am J Transplant.* 2013;13:1203–1216.

19. Deuse T, Barten C, Bara C, et al. A multi-center, randomized, open-label, parallel group Phase IV trial investigating the outcome on renal function, efficacy and safety of CNI-reduction or elimination with everolimus in de novo heart transplant recipients: the MANDELA study design [Abstract P107]. *Transpl Int.* 2014;27(Suppl 3):S46.

20. Snell GI, Valentine VG, Vitulo P, et al. Everolimus versus azathioprine in maintenance lung transplant recipients: an international, randomized, double-blind clinical trial. *Am J Transplant.* 2006;6:169–177.

21. Glanville AR, Aboyoun C, Klepetko W, et al. Three-year results of an investigator-driven multicenter, international, randomized open-label de novo trial to prevent BOS after lung transplantation. *J Heart Lung Transplant.* 2015;34:16–25.

22. Gottlieb J, Deuse T, Witt C, et al. Comparison of an innovative everolimus-containing quadruple immunosuppressive regimen versus a standard triple regimen in lung transplant recipients and its impact on renal function, safety and efficacy: the 4EVERLUNG study design. *J Heart Lung Transplant.* 2013;32(4 Suppl):S171–S172.

23. Gullestad L, Iversen M, Mortensen SA, et al. Everolimus with reduced calcineurin inhibitor in thoracic transplant recipients with renal dysfunction: a multicenter, randomized trial. *Transplantation.* 2010;89:864–872.