Month 12 Study results
CRAD001A2433

Peter Bernhardt on behalf of the TRANSFORM CTT
October 2017
A 24 month, multicenter, randomized, open-label safety and efficacy study of concentration-controlled everolimus with reduced calcineurin inhibitor vs mycophenolate with standard calcineurin inhibitor in *de novo* renal transplantation - Advancing renal TRANSplant efficacy and safety Outcomes with an eveRolimus-based regiMen (TRANSFORM)

CRAD001A2433
Several studies have shown that acute rejection is a major risk factor for long-term allograft failure in KTxRs\textsuperscript{1-4}.

Strategies that limit CNI-related nephrotoxicity while retaining IS efficacy and maximize long-term outcomes are highly desired\textsuperscript{5}.

eGFR with a cutoff of 50 mL/min/1.73 m\textsuperscript{2} at M12 is associated with increased risk of long-term graft loss\textsuperscript{6}.

TRANSFORM will determine the benefits of an EVR-based regimen with reduced CNI exposure vs an MPA based regimen with standard CNI exposure in de novo KTxRs.

TRANSFORM (Advancing Renal TRANSplant eFficacy and safety Outcomes with an eveRolimus-based regiMen) is to date the largest prospective de novo renal transplant study utilizing a novel binary composite endpoint of eGFR (<50 mL/min/1.73 m\textsuperscript{2}, MDRD4 formula) or tBPAR, that will accurately reflect the impact of IS regimen on long-term graft survival.

CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; EVR, everolimus; IS, immunosuppressive; KTxRs, kidney transplant recipients; M, month; MDRD4, 4-variable modification of diet in renal disease; MPA, mycophenolic acid; tBPAR, treated biopsy-proven acute rejection; sCNI, standard-exposure CNI.

Study design

*Stratified at RND for CNI (CsA vs TAC) and donor type (living donors, deceased standard criteria donors, and deceased expanded criteria donors)

ATG, antithymocyte globulin; Bax, basiliximab; C0, trough level; CsA, cyclosporine A; D, day; EVR, everolimus; EC-MPS, enteric-coated mycophenolate sodium; M, month; MMF, mycophenolate mofetil; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; RND, randomization; sCNI, standard-exposure calcineurin inhibitor; TAC, tacrolimus

Objectives

Primary objective at M12

To evaluate the effect of EVR+rCNI vs MPA+sCNI treatment regimen on the binary composite of tBPAR or eGFR < 50 mL/min/1.73 m² (MDRD4 formula)

Secondary objectives at M12 and M24

To evaluate

- Composite efficacy failure of - tBPAR, GL, or death; tBPAR, GL, death or eGFR < 50 mL/min/1.73 m²; tBPAR, GL or death; tBPAR, GL, death, or loss to follow-up; GL or death; tBPAR or eGFR < 50 mL/min/1.73 m² (MDRD4)
- Incidences of death, GL, tBPAR, BPAR, tAR, AR, or humoral rejection, tBPAR (excluding grade 1A rejections) or eGFR < 50 mL/min/1.73 m², tBPAR by severity and time to event, eGFR < 50 mL/min/1.73 m²
- Incidence of composite endpoint of tBPAR or eGFR < 50 mL/min/1.73 m² (MDRD4) among compliant subjects
- Incidence of composite endpoint of tBPAR or eGFR < 50 mL/min/1.73 m² (MDRD4) among subgroups

Secondary objectives at M12 and M24

Evolution of renal function (eGFR) over time by slope analysis, Change in renal allograft function from Month 1 (eGFR)

- AEs, SAEs, and AEs leading to study regimen discontinuation
- CMV infection, BKV infection, NODM, CKD with associated proteinuria, and CNI-associated AEs
- Urinary protein and albumin excretion estimated by urinary protein/creatinine and urinary albumin/creatinine ratios

Key exploratory objectives

- Incidence of DSA by treatment group, and in relation to AR, in a subset of patients
- Development of CAN/IFTA on protocol renal biopsy in a subset of patients

AE, adverse event; AR, acute rejection; BPAR, biopsy-proven acute rejection; BKV, BK virus; CAN, chronic allograft nephropathy; CKD, chronic kidney disease; CMV, cytomegalovirus; CNI, calcineurin inhibitor; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; EVR, everolimus; GL, graft loss; IFTA, Interstitial fibrosis/tubular atrophy; M, month; MACE, major adverse cardiac event; MDRD4, 4-variable modification of diet in renal disease; MPA, mycophenolic acid; NODM, new-onset diabetes mellitus; rCNI, reduced-exposure calcineurin inhibitor; SAE, serious adverse event; sCNI, standard-exposure calcineurin inhibitor; tAR, treated acute rejection; tBPAR, treated biopsy-proven acute rejection; Tx, transplantation

### Eligibility criteria

#### Key inclusion criteria

- *De novo* kidney transplant patients aged ≥18 years
- Recipients of a graft from a living or deceased heart-beating donor

#### Key exclusion criteria

- Multi-organ transplantation
- HLA-identical living-related donation
- Cold ischaemia time >30 h
- High risk of rejection (e.g., high PRA or presence of pre-existing DSA)
- Hepatitis C virus positivity
- Body mass index >35 kg/m²

†As determined by local practice for assessment of antidonor reactivity, e.g., high panel reactive antibodies, presence of pre-existing donor specific antigen

BMI, body mass index; CDC, complement-dependent lymphocytotoxic; HBsAg, hepatitis B surface antigen; HCV, hepatitis C Virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; KTx, kidney transplant; Tx, transplant; WBC, white blood cell

## Patient disposition

### Acceptable discontinuation rate for EVR

<table>
<thead>
<tr>
<th>Category</th>
<th>EVR+rCNI N = 1022</th>
<th>MPA+sCNI N = 1015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screened</strong></td>
<td>2226</td>
<td></td>
</tr>
<tr>
<td><strong>Randomized</strong></td>
<td>2044</td>
<td></td>
</tr>
<tr>
<td>Randomized but did not receive study drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misrandomized*</td>
<td>EVR+rCNI 18 (0.9%)</td>
<td>MPA+sCNI 8 (0.4%)</td>
</tr>
<tr>
<td>Discontinued study phase</td>
<td>EVR+rCNI 91 (8.9%)</td>
<td>MPA+sCNI 89 (8.8%)</td>
</tr>
<tr>
<td>Subject/guardian decision</td>
<td>EVR+rCNI 41 (4.0%)</td>
<td>MPA+sCNI 36 (3.5%)</td>
</tr>
<tr>
<td>Graft loss</td>
<td>EVR+rCNI 32 (3.1%)</td>
<td>MPA+sCNI 24 (2.4%)</td>
</tr>
<tr>
<td>Death</td>
<td>EVR+rCNI 16 (1.6%)</td>
<td>MPA+sCNI 26 (2.6%)</td>
</tr>
<tr>
<td>Technical problems</td>
<td>EVR+rCNI 1 (0.1%)</td>
<td>MPA+sCNI -</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>EVR+rCNI 1 (0.1%)</td>
<td>MPA+sCNI 3 (0.3%)</td>
</tr>
<tr>
<td>Discontinued study medication</td>
<td>EVR+rCNI 277 (27.3%)</td>
<td>MPA+sCNI 190 (18.8%)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>EVR+rCNI 214 (21.1%)</td>
<td>MPA+sCNI 115 (11.4%)</td>
</tr>
<tr>
<td>Subject/guardian decision</td>
<td>EVR+rCNI 20 (2.0%)</td>
<td>MPA+sCNI 36 (3.6%)</td>
</tr>
<tr>
<td>Graft loss</td>
<td>EVR+rCNI 16 (1.6%)</td>
<td>MPA+sCNI 20 (2.0%)</td>
</tr>
<tr>
<td>Death</td>
<td>EVR+rCNI 10 (1.0%)</td>
<td>MPA+sCNI 11 (1.1%)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>EVR+rCNI 12 (1.2%)</td>
<td>MPA+sCNI 2 (0.2%)</td>
</tr>
<tr>
<td>Technical problems</td>
<td>EVR+rCNI 3 (0.3%)</td>
<td>MPA+sCNI 4 (0.4%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>EVR+rCNI 2 (0.2%)</td>
<td>MPA+sCNI 2 (0.2%)</td>
</tr>
<tr>
<td>Completed study phase</td>
<td>EVR+rCNI 925 (90.5%)</td>
<td>MPA+sCNI 922 (90.8%)</td>
</tr>
<tr>
<td>Completed study medication</td>
<td>EVR+rCNI 737 (72.7%)</td>
<td>MPA+sCNI 822 (81.2%)</td>
</tr>
</tbody>
</table>

*one miscoded patient received study medication

EVR, everolimus; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor

Baseline data – Recipient characteristics [1/2]

Recipients’ characteristics were well balanced between the groups

Full analysis set – M12

*Others includes Black, Asian, Native American, Pacific Islander, unknown, and other; †N = 1014
BMI, body mass index; EVR, everolimus; HLA, human leukocyte antigen; M, month; MPA, mycophenolic acid; PRA, panel reactive antibody; rCNI, reduced-exposure calcineurin inhibitor; rATG, rabbit antithymocyte globulin; sCNI, standard-exposure calcineurin inhibitor

Baseline data – Recipient characteristics [2/2]

Recipients’ characteristics were well balanced between the groups

*Others includes Black, Asian, Native American, Pacific Islander, unknown, and other; †N = 1014
EVR, everolimus; HLA, human leukocyte antigen; M, month; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor
**Baseline data – Donor characteristics**

*Donors’ baseline characteristics were comparable between the groups*

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**Mean Age (years)**
- EVR+rCNI (N = 1022): 49.5
eVR+rCNI (N = 1022): 48.4
- MPA+sCNI (N = 1015): 49.8

**Incidence (%)**
- Male: 48.2
- Male: 50

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**EVR+rCNI (N = 1022)**
- Deceased non-heart beating: 0.5
- Deceased heart beating: 20.5
- Living unrelated: 29.5
- Living related: 18.9

**MPA+sCNI (N = 1015)**
- Deceased non-heart beating: 0.3
- Deceased heart beating: 18.9
- Living unrelated: 31
- Living related: 18.9

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**EVR+rCNI (N = 1022)**
- Asian: 27.6
- Caucasian: 60.7
- Others*: 11.7

**MPA+sCNI (N = 1015)**
- Asian: 27.8
- Caucasian: 59
- Others*: 13.2

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**EVR+rCNI (N = 1022)**
- SCD: 30
- ECD: 70

**MPA+sCNI (N = 1015)**
- SCD: 31.7
- ECD: 68.3

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*Others include Black, Native American, Pacific Islander, unknown, other, and missing
†Percentage is relative the number of deceased heart beating donors
EVR, everolimus; M, month; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor
SD, standard deviation;
Primary disease leading to KTx

Glomerular disease and polycystic disease were the leading causes

EVR+rCNI (N = 1022)  MPA+sCNI (N = 1015)

*Others include pyelonephritis, drug induced toxicity, interstitial nephritis, vasculitis, obstructive disorder/reflux, renal hypoplasia/dysplasia, unknown, missing, and other EVR, everolimus; IgA, immunoglobulin A; KTx, kidney transplantation; M, month; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor.
Efficacy outcomes
Primary efficacy endpoint

**EVR+rCNI was non-inferior to MPA+sCNI**

*P value to test for no difference ([EVR+rCNI] – [MPA+sCNI] = 0); **P value for non-inferiority test (non-inferiority margin = 10%) is for one-sided test and should be compared to 0.025 significance level; The *P* value of the interaction between CNI and treatment (EVR vs MPA) from a logistic regression model was 0.345

†Endpoint compared using raw incidence rates; Imputation for missing eGFR (MDRD4) values: assigned a value of zero for missing due to graft loss; otherwise, imputed using the multiple imputation method then the eGFR value is dichotomized to derive the component of eGFR (MDRD4) <50 mL/min/1.73 m² CI, confidence interval; CNI, calcineurin inhibitor; Diff, difference; eGFR, estimated glomerular filtration rate; EVR, everolimus; FAS, full analysis set; MDRD4, 4-variable modification of diet in renal disease; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor; tBPAR, treated biopsy-proven acute rejection

Pascual J, et al. [#LOS001] 18th Congress of ESOT, 2017

<table>
<thead>
<tr>
<th>Control-based imputation for missing eGFR</th>
<th>EVR+rCNI N = 1022</th>
<th>MPA+sCNI N = 1015</th>
<th>Difference (95% CI)</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &lt; 50 mL/min/1.73 m² or tBPAR†, n (%)</td>
<td>491 (48.0)</td>
<td>457 (45.0)</td>
<td>3.0 (−1.4, 7.4)</td>
<td>0.185</td>
</tr>
</tbody>
</table>

Multiple imputation for missing eGFR

![Graph showing incidence of composite of eGFR < 50 mL/min/1.73 m² or tBPAR (%)](image)

- EVR+rCNI: 48.2%
- MPA+sCNI: 45.1%

**P** = 0.001

*P* = 0.160

Diff (95% CI)

3.2 (−1.3, 7.6)
## Secondary efficacy endpoint and components

**EVR+rCNI was non-inferior to MPA+sCNI**

<table>
<thead>
<tr>
<th>Secondary efficacy endpoint, FAS</th>
<th>EVR+rCNI N = 1022</th>
<th>MPA+sCNI N = 1015</th>
<th>Difference (95% CI)</th>
<th>P* value</th>
<th>P** value</th>
</tr>
</thead>
<tbody>
<tr>
<td>tBPAR, graft loss or death, n (KM %)</td>
<td>137 (14.9)</td>
<td>122 (12.5)</td>
<td>2.3 (−1.7, 6.4)</td>
<td>0.252</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Composite efficacy failure includes tBPAR, graft loss, or death; *P value for difference is from z-test statistic for no difference (EVR+rCNI – [MPA+sCNI] = 0); **P value for non-inferiority test (non-inferiority margin = 10%) is for one-sided test and should be compared to 0.025 significance level.

KM event rate and 95% CI for each treatment are obtained using KM probability estimates of efficacy failure rates and standard error derived based on Greenwood’s formula.

In KM estimate, patients without an event are censored at the last contact day.

CI, confidence interval; CNI, calcineurin inhibitor; EVR, everolimus; FAS, full analysis set; KM, Kaplan-Meier; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor; tBPAR, treated biopsy-proven acute rejection.

Other secondary efficacy endpoints

**EVR+rCNI was non-inferior to MPA+sCNI**

Full analysis set – M12

- **P** *< 0.001
- Diff (95% CI)
- 2.0 (−2.2, 6.1)
- 17.8
- 15.8

- **P** *< 0.001
- Diff (95% CI)
- 2.4 (−1.7, 6.4)
- 15.3
- 12.9

- **P** *< 0.001
- Diff (95% CI)
- 2.8 (−1.1, 6.6)
- 12.0
- 9.2

- **P** *< 0.001
- Diff (95% CI)
- 3.0 (−0.5, 6.5)
- 8.1
- 5.1

- **P** *< 0.001
- Diff (95% CI)
- 0.4 (−2.7, 3.5)
- 13.8
- 13.4

- **P** *< 0.001
- Diff (95% CI)
- 0.8 (−2.1, 3.8)
- 12.5
- 11.7

- **P** *< 0.001
- Diff (95% CI)
- 2.0 (−1.5, 5.5)
- 7.8
- 5.8

- **P** *< 0.001
- Diff (95% CI)
- −0.5 (−1.4, 0.4)
- 0.7
- 1.2

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**P** value for non-inferiority test (non-inferiority margin = 10%) is for one-sided test and should be compared to 0.025 significance level.

KM event rate and 95% CI for each treatment are obtained using KM probability estimates of efficacy failure rates and standard error derived based on Greenwood's formula. In KM estimate, patients without an event are censored at the last contact day.

AMR, antibody-mediated rejection; AR, acute rejection; BPAR, biopsy-proven acute rejection; cAMR, chronic active antibody-mediated rejection; CI, confidence interval; EVR, everolimus; FAS, full analysis set; GL, graft loss; KM, Kaplan-Meier; LFUP, loss to follow up; M, month; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor; tAR, treated acute rejection; tBPAR, treated biopsy-proven acute rejection.

Evolution of eGFR (MDRD4 formula)

Mean eGFR was similar between EVR+rCNI and MPA+sCNI groups

Multiple imputation for missing eGFR data

Mean difference in eGFR at M12: −1.39 (−3.29, 0.51)

Mean and SE of eGFR
Imputation for missing eGFR (MDRD4) values: assigned a value of zero for missings due to graft loss; otherwise, imputed using the multiple imputation method
BL, baseline; eGFR, estimated glomerular filtration rate; EVR, everolimus; M, month; MDRD4, 4-variable modification of diet in renal disease; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor; SE, standard error; W, week
Pascual J, et al. [#LOS001] 18th Congress of ESOT, 2017
Safety outcomes
## Overall AEs

**Overall, comparable events rates but higher study medication discontinuations in EVR+rCNI vs MPA+sCNI group**

<table>
<thead>
<tr>
<th>Preferred term, n (%)</th>
<th>EVR+rCNI (N = 1014)</th>
<th>MPA+sCNI (N = 1012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE/infection</td>
<td>993 (97.9)</td>
<td>984 (97.2)</td>
</tr>
<tr>
<td>Any notable event†</td>
<td>595 (58.7)</td>
<td>586 (57.9)</td>
</tr>
<tr>
<td>Non-fatal SAE/infection†</td>
<td>554 (54.6)</td>
<td>558 (55.1)</td>
</tr>
<tr>
<td>AE/infection leading to study medication discontinuation†</td>
<td>233 (23.0)</td>
<td>120 (11.9)</td>
</tr>
<tr>
<td>Death†</td>
<td>16 (1.6)</td>
<td>26 (2.6)</td>
</tr>
</tbody>
</table>

**AEs of Interest**

<table>
<thead>
<tr>
<th>Event</th>
<th>EVR+rCNI (N = 1014)</th>
<th>MPA+sCNI (N = 1012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral oedema</td>
<td>321 (31.7)</td>
<td>224 (22.1)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>236 (23.3)</td>
<td>260 (25.7)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>94 (9.3)</td>
<td>192 (19.0)</td>
</tr>
<tr>
<td>Increased blood creatinine</td>
<td>162 (16.0)</td>
<td>144 (14.2)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>137 (13.5)</td>
<td>146 (14.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>129 (12.7)</td>
<td>119 (11.8)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>128 (12.6)</td>
<td>57 (5.6)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>120 (11.8)</td>
<td>59 (5.8)</td>
</tr>
</tbody>
</table>

Notable events include death, non-fatal SAE/infection and AE/infection leading to study medication discontinuation

AE, adverse event; EVR, everolimus; M, month; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; SAE, serious adverse event; sCNI, standard-exposure calcineurin inhibitor

Pascual J, et al. [#LOS001] 18th Congress of ESOT, 2017
Wound complications (≥ 2% in any group)

Overall, wound complications were more frequent with EVR+rCNI vs MPA+sCNI

A subject with multiple occurrences of a level under one treatment is counted only once for the same risk for that treatment.

Used MedDRA version 20.0 and RAD001 Compound Case Retrieval strategy definition for indication Kidney, heart and liver transplant active from 2017-04-30

EVR, everolimus; M, month; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor

Citterio F et al. [abstract ID #599] 27th International Congress of TTS, 2018
Infections (≥5% in any group)

**EVR+rCNI offers protection from viral infections**

Safety analysis set – M12

The dictionary used is the SNOMED.
Preferred terms for micro-organisms are alphabetically sorted within each type of infection.
A patient with multiple occurrences of an infection is counted only once in the infection category.
A patient with multiple infections within a type of organism is counted only once in the Total row.
BKV, BK virus; CMV, cytomegalovirus; EVR, everolimus; M, month; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor.
Cruzado J, et al. [LOS002] 18th Congress of ESOT, 2017
# CMV infections

**Low incidence of CMV infection including syndrome and disease with EVR+rCNI**


## Safety analysis set – M12

<table>
<thead>
<tr>
<th>CMV events, n (%)</th>
<th>EVR+rCNI N = 1014</th>
<th>MPA+sCNI N = 1012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of CMV infection</td>
<td>40 (3.9)</td>
<td>113 (11.2)</td>
</tr>
<tr>
<td>CMV syndrome</td>
<td>15 (1.5)</td>
<td>50 (4.9)</td>
</tr>
<tr>
<td>Histological signs for CMV</td>
<td>1 (0.1)</td>
<td>6 (0.6)</td>
</tr>
<tr>
<td>Histological organ examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Kidney</td>
<td>2 (0.2)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>Liver</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lung</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>30 (3.0)</td>
<td>50 (4.9)</td>
</tr>
<tr>
<td>Biopsy performed</td>
<td>5 (0.5)</td>
<td>18 (1.8)</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; EVR, everolimus; M, month; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor.
## BKV infections

**Low incidence with EVR+rCNI**

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>EVR+rCNI N = 1014</th>
<th>MPA+sCNI N = 1012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any BKV infection</td>
<td>77 (7.6)</td>
<td>126 (12.5)</td>
</tr>
<tr>
<td>BKV infection with a urinary or serological sign</td>
<td>77 (7.6)</td>
<td>126 (12.5)</td>
</tr>
<tr>
<td>Clinical or laboratory-indicated BKV infection</td>
<td>34 (3.4)</td>
<td>58 (5.7)</td>
</tr>
<tr>
<td>BKV infection with an organ involvement (histological evidence)</td>
<td>12 (1.2)</td>
<td>21 (2.1)</td>
</tr>
</tbody>
</table>

BKV, BK virus; EVR, everolimus; M, month; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor

Summary

**Primary endpoint achieved**

### Drug exposure
- 64% of the patients achieved target EVR $C_0$ as early as W1
- Up to 44% of the patients were above target TAC $C_0$ in the EVR+rTAC group

### Efficacy
- Non-inferiority of EVR+rCNI over MPA+sCNI achieved for:
  - Primary efficacy endpoint of binary composite of eGFR < 50 mL/min/1.73 m$^2$ or tBPAR (difference, 3.2%; 95% CI, −1.3 to 7.6; $P = 0.001$)
  - Secondary efficacy endpoint of tBPAR, graft loss, or death (difference, 2.3%; 95% CI, −1.7 to 6.4; $P < 0.001$)
- Overall incidence of tBPAR was low
- Comparable mean eGFR (MDRD4) over 12 months between EVR+rCNI and MPA+sCNI groups

### Safety
- Overall, comparable incidence of AEs and SAEs in the EVR+rCNI vs the MPA+sCNI group. No new safety signals detected
- Higher rates of study medication discontinuation due to AEs/infection in the EVR+rCNI vs the MPA+sCNI (23.0% vs 11.9%) group
- Higher incidence of proteinuria (12.6% vs 5.6%) and hyperlipidemia (11.8% vs 5.8%) in the EVR+rCNI vs the MPA+sCNI group
- Lower CMV (3.6% vs 13.3%) and BKV infection rates (4.3% vs 8.0%) in the EVR+rCNI vs the MPA+sCNI group
- Lower incidence of death in the EVR+rCNI (n = 16, 1.6%) vs the MPA+sCNI (n = 26, 2.6%) group
  - Cardiac disorders (EVR+rCNI, n = 6; MPA+sCNI, n = 6) and infections and infestations (EVR+rCNI, n = 5; MPA+sCNI, n = 7) were the major reason of deaths
Conclusions

Overall, the 12-month results from TRANSFORM study in 2037 de novo kidney transplant recipients suggest that everolimus-based regimen offers comparable efficacy and renal outcomes, with safety findings consistent with the known safety profile of everolimus.