CRAD001H2307 Study
(NCT01888432)

Results at Month 12
The purpose of the H2307 study

• To demonstrate the efficacy and safety of EVR in combination with reduced TAC vs standard TAC in living-donor liver transplant recipients

• To support the registration of EVR in liver transplantation in Japan
Relevance of the H2307 study

• Designed as a registrational study for Japan, it is the only randomized, controlled, international study comparing two treatment regimens in living-donor liver transplantation which fulfills the strictest criteria for study conduct and data collection

• Hepatocellular carcinoma (HCC) recurrence has become the main unmet medical need in liver transplantation after the advent of new drugs to prevent HCV recurrence

• H2307 provides a unique opportunity to evaluate the impact of EVR on HCC recurrence in a population with high prevalence of HCC
H2307 will fill the data gaps from H2304

<table>
<thead>
<tr>
<th></th>
<th>H2304 study</th>
<th>H2307 study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment groups</td>
<td>EVR+reduced TAC vs TAC</td>
<td>Same (± basiliximab induction)</td>
</tr>
<tr>
<td>Type of donor</td>
<td>Deceased</td>
<td>Living</td>
</tr>
<tr>
<td>Study allocation</td>
<td>No sites in Asia</td>
<td>Asia is main contributor</td>
</tr>
<tr>
<td>Liver disease</td>
<td>20% HCC 7% HBV+</td>
<td>42% HCC 14% HBV+</td>
</tr>
<tr>
<td>Inclusion criteria for patients with HCC</td>
<td>The strictest: Milan criteria based on explanted liver examination (rather than by imaging pre-Tx)</td>
<td>More liberal: all HCC (regardless of number of nodules and sizes) except tumors with macrovascular invasion or extrahepatic spread</td>
</tr>
</tbody>
</table>

EVR, everolimus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TAC, tacrolimus; Tx, transplantation
**Study design**

- **Basiliximab or no induction**
- **Run-in period 4 weeks**
- **TAC (C<sub>0</sub>: 5-15 ng/mL) + MPA* + CS**
- **RND (1:1)**
- **EVR + reduced TAC**
  - **EVR (C<sub>0</sub>: 3-8 ng/mL)**
  - **Reduced TAC C<sub>0</sub>: 3-5 ng/mL**
- **Controls**
  - **Standard-dose TAC**
  - **TAC C<sub>0</sub>: 8-12 ng/mL**
  - **TAC C<sub>0</sub>: 6-10 ng/mL**

* As per center practice
** Corticosteroids in both arms as per local practice
CS, corticosteroid; EVR, everolimus; MPA, mycophenolic acid; RND, randomization; TAC, tacrolimus; Tx, transplantation

Key inclusion criteria

- Age ≥18 years
- Recipient of a primary, orthotopic liver allograft from a living donor
- Known HCV and HBV status, and HIV negative
- Initiated on TAC-based immunosuppressive regimen
- Allograft condition acceptable at time of randomization (AST, ALT and total bilirubin levels ≤3 times ULN)
- Estimated GFR (eGFR) ≥30 mL/min/1.73m² (MDRD-4)
Key exclusion criteria at study entry

• Transplantation for acute liver failure (patients with acute on chronic liver failure were eligible)

• HCV negative recipient with a graft from a HCV+ donor

• Multiple solid organ (including multiple liver lobes/segments) or islet cell transplants, or previous organ or tissue transplant

• ABO incompatible allograft

• MELD score >35 within 1 month prior to transplant

• History of malignancy of any organ system (except HCC or localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years

• HCC with extrahepatic spread or macrovascular invasion

• Pregnant or nursing (lactating) women
Key exclusion criteria at randomization

- Post-transplant thrombosis, occlusion or stent placement in any hepatic arteries, hepatic veins, portal vein or inferior vena cava at any time during the pre-randomization run-in period.
- Spot urine protein/creatinine ratio $\geq 1.0$ g/24 hrs.
- Severe hypercholesterolemia ($>350$ mg/dL; $>9.1$ mmol/L) or hypertriglyceridemia ($>500$ mg/dL; $>5.6$ mmol/L).
- Detectable HBV DNA.
- Any acute rejection in the week prior to randomization.
- 2 treated acute rejections.
- Any rejection requiring antibody treatment.
- Any severe cellular (and/or any humoral) rejection (RAI $\geq 7$).

HBV, hepatitis B virus; DNA, deoxyribonucleic acid; RAI, rejection activity index.
Key exclusion criteria – donor liver

- Full-size, split, auxiliary, dual and or/domino liver allografts
- Small-for-size allograft (allograft to recipient weight ratio <0.7% or a liver volume <30% of standard:estimated volume)
- HIV-positive donors
- HBsAg-positive donors
- Donor with hepatic steatosis >30%
Study objectives

Primary objective

- To demonstrate **comparable efficacy** as measured by the composite efficacy failure of treated biopsy-proven acute rejection (tBPAR), graft loss or death at 12 months post-transplant

Key secondary objective

- To demonstrate at least **comparable renal function**, measured by change in estimated GFR (eGFR) from randomization to month 12 post-transplant
Patient population
Baseline characteristics

Balanced between treatment groups

**ITT set**

- EVR+rTAC (N=142)
- TAC Control (N=142)

BMI, body mass index; eGFR, estimated glomerular filtration rate; EVR, everolimus; HBV, hepatitis B virus; HCV, hepatitis C Virus; ITT, intent-to-treat; MDRD4, 4-variable Modification of Diet in Renal Disease; rTAC, reduced-dose tacrolimus; SD, standard deviation; TAC-C, tacrolimus control

Liver transplantation history

*HCC was the most frequent reason for transplantation*

**ITT set**

*Other includes amyloidosis, autoimmune hepatitis, biliary atresia, Budd-Chiari syndrome, hemochromatosis, metabolic disease, polycystic liver disease, and other.*

EVR, everolimus; HCC, hepatocellular carcinoma; MELD, Model for End-stage Liver Disease; NASH, non-alcoholic steatohepatitis; rTAC, reduced-dose tacrolimus; TAC-C, tacrolimus control

Donor characteristics

Balanced between treatment groups

EVR, everolimus; ITT, intent-to-treat; rTAC, reduced-dose tacrolimus; SD, standard deviation; TAC-C, tacrolimus control
Mean EVR trough levels

Target levels were reached quickly and maintained

EVR trough level (ng/mL), mean (SD)

Time post-transplant

No. patients

C₀, trough level; EVR, everolimus; M, month; W, week

Mean TAC trough levels
Above or near the upper limit in EVR+reduced TAC group

<table>
<thead>
<tr>
<th>Time post transplant</th>
<th>Mean TAC trough levels (ng/mL)</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>EVR+rTAC</td>
<td>n</td>
</tr>
<tr>
<td>W5</td>
<td></td>
<td>125</td>
<td>6.6</td>
<td>32</td>
</tr>
<tr>
<td>W6</td>
<td></td>
<td>132</td>
<td>5.6</td>
<td>133</td>
</tr>
<tr>
<td>M2</td>
<td></td>
<td>131</td>
<td>5.3</td>
<td>130</td>
</tr>
<tr>
<td>M3</td>
<td></td>
<td>133</td>
<td>5.2</td>
<td>130</td>
</tr>
<tr>
<td>M4</td>
<td></td>
<td>127</td>
<td>5.3</td>
<td>128</td>
</tr>
<tr>
<td>M6</td>
<td></td>
<td>126</td>
<td>4.9</td>
<td>128</td>
</tr>
<tr>
<td>M9</td>
<td></td>
<td>122</td>
<td>4.4</td>
<td>121</td>
</tr>
<tr>
<td>M12</td>
<td></td>
<td>121</td>
<td>4.4</td>
<td>115</td>
</tr>
</tbody>
</table>

36% reduction in TAC exposure (EVR+rTAC vs TAC-C) at M12
Primary endpoint
Primary efficacy endpoint

Comparable between treatment groups

<table>
<thead>
<tr>
<th>KM estimate of incidence rate of composite efficacy failure (tBPAR, graft loss or death) at M12, n %</th>
<th>EVR+rTAC (N=142)</th>
<th>TAC Control (N=142)</th>
<th>% Difference (90% CI)</th>
<th>P value for non-inferiority (EVR/rTAC vs TAC Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7 (5.1)</td>
<td>8 (5.8)</td>
<td>-0.7 (-5.2, 3.7)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

- Non inferiority achieved for EVR+rTAC vs TAC Control
- The upper limit of the CI for the difference was less than 12%, the pre-specified non-inferiority (NI) margin (one-sided level of significance of 5%)
- KM estimates log rank $P = 0.805$

CI, confidence interval; EVR, everolimus; ITT, intent-to-treat; M, month; NI, non-inferiority; rTAC, reduced-dose tacrolimus; TAC-C, tacrolimus control; tBPAR, treated biopsy-proven acute rejection
Secondary efficacy endpoints
Kaplan-Meier incidence rates for components of the composite efficacy endpoint

All components were similar between groups

EVR, everolimus; ITT, intent-to-treat; rTAC, reduced-dose tacrolimus; TAC-C, tacrolimus control; tBPAR, treated biopsy-proven acute rejection

Incidence & severity of tBPAR (RAI)

Fewer severe rejections in EVR+rTAC group vs TAC Controls

- No patient had ≥1 episode of tBPAR

EVR, everolimus; ITT, intent-to-treat; RAI, rejection activity index; rTAC, reduced-dose tacrolimus; TAC-C, tacrolimus control; tBPAR, treated biopsy-proven acute rejection

Renal function
Comparison of renal function endpoint: change in eGFR (MDRD-4)
Comparable between groups at month 12

### Safety set

<table>
<thead>
<tr>
<th></th>
<th>LS mean (SE)</th>
<th>Difference (EVR+rTAC – TAC Control)</th>
<th>One-sided p-value for non-inferiority</th>
<th>Two-sided p-value for superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LS mean (SE)</td>
<td>90% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVR+rTAC (N=142)</td>
<td>-8.0 (1.8)</td>
<td>4.2 (2.6)</td>
<td>(-0.1, 8.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TAC Control (N=142)</td>
<td>-12.1 (1.8)</td>
<td></td>
<td></td>
<td>0.108</td>
</tr>
</tbody>
</table>

- Non-inferiority for renal function was achieved for EVR+rTAC against TAC Control for a pre-specified non inferiority (NI) margin of −6 mL/min/1.73m² (one-sided level of significance 5%)
- Superiority of EVR+rTAC group was not demonstrated

LS means, 90% CI, and P-values are from an ANCOVA model containing treatment, pre-transplant HCC status and eGFR at RND as a covariate

ANCOVA, analysis of covariance; CI, confidence interval; eGFR, estimated glomerular filtration rate; EVR, everolimus; LS, least square; MDRD4, 4-variable Modification of Diet in Renal Disease; RND, randomization; rTAC, reduced-dose tacrolimus; SE, standard error; TAC-C, tacrolimus control

**Evolution of mean eGFR (MDRD-4)**

*Numerically or significantly higher eGFR in EVR+TAC at all study visits*

<table>
<thead>
<tr>
<th>Time post transplant</th>
<th>Mean eGFR (MDRD4; mL/min/1.73m^2)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EVR+rTAC</td>
<td>TAC-C</td>
</tr>
<tr>
<td>RND</td>
<td>89.9</td>
<td>89.7</td>
</tr>
<tr>
<td>W6</td>
<td>99.1</td>
<td>86.1</td>
</tr>
<tr>
<td>M2</td>
<td>92.9</td>
<td>82.1</td>
</tr>
<tr>
<td>M3</td>
<td>87.5</td>
<td>79.5</td>
</tr>
<tr>
<td>M4</td>
<td>85.2</td>
<td>76.5</td>
</tr>
<tr>
<td>M6</td>
<td>83.6</td>
<td>75.9</td>
</tr>
<tr>
<td>M9</td>
<td>81.7</td>
<td>76.0</td>
</tr>
<tr>
<td>M12</td>
<td>81.2</td>
<td>76.5</td>
</tr>
</tbody>
</table>

*P value of Wilcoxon Rank-sum test

eGFR, estimated glomerular filtration rate; EVR, everolimus; ITT, intent-to-treat; M, month; MDRD4, 4-variable Modification of Diet in Renal Disease; RND, randomization; rTAC, reduced-dose tacrolimus; TAC-C, tacrolimus control; W, week

HCC-related endpoints
HCC baseline characteristics
Similar between groups

Safety set

Milan Criteria

- EVR+rTAC (N=56)
  - Yes: 21.4%
  - No: 19.4%
  - Missing: 11.3%
- TAC Control (N=62)
  - Yes: 71.4%
  - No: 69.4%
  - Missing: 0%

Number of lesions
- EVR+rTAC (N=56)
  - Median: 1
  - Range: (0–16)
- TAC Control (N=62)
  - Median: 2
  - Range: (1–33)

Diameter of largest tumor, cm
- EVR+rTAC (N=56)
  - Median: 2.1
  - Range: (0–8)
- TAC Control (N=62)
  - Median: 2.5
  - Range: (1–33)

Total tumor diameter, cm
- EVR+rTAC (N=56)
  - Median: 3.1
  - Range: (0–8)
- TAC Control (N=62)
  - Median: 3.5
  - Range: (1–33)

Alpha fetoprotein prior to transplant

- EVR+rTAC (N=56)
  - Yes: 21.4%
  - No: 1.8%
  - Missing: 1.6%
- TAC Control (N=62)
  - Yes: 76.8%
  - No: 79%
  - Missing: 0%

- EVR+rTAC (N=56)
  - Median: 11.7
  - Range: (1–2,390)
- TAC Control (N=62)
  - Median: 11.1
  - Range: (0–37,088)

EVR, everolimus; HCC, hepatocellular carcinoma; rTAC, reduced tacrolimus; SD, standard deviation; TAC, tacrolimus
HCC recurrence
Only observed in TAC Control group

<table>
<thead>
<tr>
<th></th>
<th>EVR+rTAC, n (%) (N=142)</th>
<th>TAC Control, n (%) (N=141)</th>
<th>EVR+rTAC – TAC Control (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with HCC recurrence</td>
<td>0 (0.0)</td>
<td>5 (3.5)</td>
<td>−8.1 (−25.8, 10.2)</td>
<td>0.059</td>
</tr>
<tr>
<td>Milan criteria – yes</td>
<td>0/40</td>
<td>2/43</td>
<td>−4.7 (−26.0, 16.8)</td>
<td>0.495</td>
</tr>
<tr>
<td>Milan criteria – no</td>
<td>0/4</td>
<td>3/7</td>
<td>−42.9 (−83.7, 22.7)</td>
<td>0.236</td>
</tr>
<tr>
<td>Milan criteria – missing</td>
<td>0/12</td>
<td>0/12</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Location**

<table>
<thead>
<tr>
<th>Location</th>
<th>EVR+rTAC, n (%) (N=142)</th>
<th>TAC Control, n (%) (N=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic location</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Extrahepatic location</td>
<td>0 (0.0)</td>
<td>5 (3.5)</td>
</tr>
<tr>
<td>Lung</td>
<td>0 (0.0)</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Bone</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
</tr>
</tbody>
</table>

**Death due to HCC recurrence**

| Death due to HCC recurrence | EVR+rTAC, n (%) (N=142) | TAC Control, n (%) (N=141) | - | - |

**Discontinuation of study drug due to HCC recurrence**

| Discontinuation of study drug due to HCC recurrence | EVR+rTAC, n (%) (N=142) | TAC Control, n (%) (N=141) | - | - |

- Time to recurrence and tumor-free survival could not be compared between groups since there were no events in the EVR/reduced TAC arm.
Safety endpoints
Most frequent AE/infections (≥10% in either group)

More AEs reported for EVR+rTAC

Safety set

- Hepatic enzyme abnormal
- Cough
- Headache
- Nasopharyngitis
- Hepatic enzyme increased
- Leukopenia
- Insomnia
- Upper respiratory tract infection
- Diarrhea
- Abdominal pain
- Pruritus
- Hyperlipidemia
- Hypercholesterolemia
- Pyrexia
- Hypertension
- Any AE/infection

Incidence (%)

TAC Control N = 141
EVR+rTAC N = 142

AE, adverse event; EVR, everolimus; rTAC, reduced tacrolimus; TAC, tacrolimus
Imbalanced AE/infections (difference ≥5%)
As expected for EVR and TAC safety profiles

<table>
<thead>
<tr>
<th>Primary system organ class</th>
<th>EVR+rTAC, n (%) (N=142)</th>
<th>TAC Control, n (%) (N=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE/ infection</td>
<td>139 (97.9)</td>
<td>126 (89.4)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>35 (24.6)</td>
<td>28 (19.9)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>16 (11.3)</td>
<td>6 (4.3)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12 (8.5)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>80 (56.3)</td>
<td>63 (44.7)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>18 (12.7)</td>
<td>10 (7.1)</td>
</tr>
<tr>
<td>Mouth ulceration</td>
<td>14 (9.9)</td>
<td>6 (4.3)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>14 (9.9)</td>
<td>5 (3.5)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>72 (50.7)</td>
<td>59 (41.8)</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>17 (12.0)</td>
<td>7 (5.0)</td>
</tr>
<tr>
<td>Investigations</td>
<td>50 (35.2)</td>
<td>60 (42.6)</td>
</tr>
<tr>
<td>Hepatic enzyme abnormal</td>
<td>7 (4.9)</td>
<td>15 (10.6)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>74 (52.1)</td>
<td>55 (39.0)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>19 (13.4)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>19 (13.4)</td>
<td>5 (3.5)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>36 (25.4)</td>
<td>29 (20.6)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>4 (2.8)</td>
<td>11 (7.8)</td>
</tr>
</tbody>
</table>

AE, adverse event; EVR, everolimus; rTAC, reduced tacrolimus; TAC, tacrolimus
Summary & conclusions
H2307: Summary of results at month 12

Primary and key secondary endpoints achieved

• **Efficacy**
  – Non inferiority achieved for EVR+rTAC against TAC Control for the composite efficacy failure endpoint of tBPAR, graft loss or death (primary endpoint)
  – Numerically fewer and less severe tBPAR with EVR+rTAC
  – No graft loss and balanced (low) mortality

• **Renal function**
  – Non inferiority (key secondary endpoint) and numerically better renal function achieved for EVR+rTAC in the overall analysis
  – Significant difference in eGFR in favor of EVR+rTAC in the on-treatment analysis

• **Safety**
  – Low rate of EVR+rTAC discontinuation compared to previous EVR studies and comparable to TAC Control group
  – More AEs reported for EVR+rTAC but these were not unexpected for this disease indication and patient population
  – Safety findings consistent with the known safety profile of both EVR and tacrolimus

• **Exposure**
  – Good adherence to EVR target levels
  – TAC trough was frequently above target in EVR+rTAC while below target in TAC Control (may explain not achieving superiority in main analysis of renal function)

• **HCC recurrence**
  – HCC recurrence occurred only in the TAC Control group; may indicate prevention of HCC recurrence by EVR (confirming previous evidences)
Conclusions

• Overall, results from the H2307 study show that EVR+rTAC is a valid immunosuppressive regimen in living-donor liver transplant recipients, consistent with findings from the pivotal study H2304 in deceased donor liver transplant recipients.