Pharmacokinetics and Pharmacodynamics in Mycophenolic Acid Derivates

Sotrastaurin

Federico Oppenheimer

Head of the Renal Transplant Unit

Nephrology and Renal Transplant Service

Hospital Clinic, Barcelona, Spain

oppen@clinic.ub.es
Introduction

- Mycophenolic acid (MPA) is the most widely used antimetabolite in solid organ transplantation
- Patients on standard-dose MPA therapy show considerable between-patient variability in pharmacokinetic parameters\(^1\)
- There is a significant relationship between exposure early after transplantation and BPAR during the first month\(^2,3\)
- Oral bioavailability of MPA may be affected by the interaction of other drugs concomitantly administered in the initial transplant period\(^4\)

\(^3\) Van Gelder T et al. Transplantation 2008;86: 1043
Use of PPIs in transplant recipients

- PPIs are commonly used to combat GI adverse events in transplant recipients\(^1\)
- Drug-drug interactions are potentially an overlooked issue
  - Data are emerging regarding the interaction between MPA and PPIs\(^2\)


PPI, proton pump inhibitor; GI, gastrointestinal; MPA, mycophenolic acid; CsA, cyclosporin
Proton pump inhibitor co-medication and potential implications for MPA dosing and outcomes

- PPIs and the consequences for MPA AUC
  - With MMF
  - With EC-MPS
- MPA AUC and efficacy
- Efficacy of EC-MPS vs MMF
PPI co-medication and potential implications for MPA dosing and outcomes

- PPIs and the consequences for MPA AUC
  - With MMF
  - With EC-MPS
- MPA AUC and efficacy
- Efficacy of EC-MPS vs MMF

PPI, proton pump inhibitor; MPA, mycophenolic acid; AUC, area under the concentration-time curve; MMF, mycophenolate mofetil; EC-MPS, enteric-coated mycophenolate sodium
MMF-derived MPA dissolution is dependent on stomach pH

MMF is released in the stomach at pH <3

● PPIs can increase gastric pH to >4

MMF dissolves only in acidic conditions

Solubility (µg/mL)

- MMF, mycophenolate mofetil; MPA, mycophenolic acid; PPI, proton pump inhibitor
MPA exposure is reduced by concomitant PPI and MMF treatment\(^a\) in healthy volunteers

---

**Plasma concentration-time course of MPA following single oral dose of MMF 1000 mg with or without 40 mg pantoprazole (n=12)**

\[\text{MPA (µg/mL)}\]

\[\text{Time (h)}\]

---

\(\text{MMF}\)

\(\text{MMF / pantoprazole}\)

---

\(\text{Following a single oral dose of MMF 1000 mg (equivalent to 720 mg MPA)\nMPA, mycophenolic acid; PPI, proton pump inhibitor;\nEC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil}\)

---

PPIs reduce MPA exposure in heart transplant recipients treated with MMF (1)

MMF plasma concentration-time profiles of MPA in patients with / without pantoprazole

Values reported as mean ± standard deviation; each parameter was statistically compared with control
*p=0.004; **p=0.001 vs control
PPI, proton pump inhibitor; MPA, mycophenolic acid; MMF, mycophenolate mofetil

PPIs reduce MPA exposure in heart transplant recipients treated with MMF (2)

*Mean MPA AUC (mg x h/L) (4-point limited sampling strategy)*

Control without PPI

With pantoprazole

MPA AUC measurements with / without 40 mg of pantoprazole

*+34% decrease*

*p=0.003 vs control*

PPI, proton pump inhibitor; MPA, mycophenolic acid; AUC, area under the concentration-time curve

MPA exposure is also reduced in renal transplant patients receiving MMF and PPIs

Retrospective analysis of mean dose-adjusted $C_{\text{max}}$ of MPA 1 year after renal transplant in patients receiving MMF / tacrolimus or MMF / tacrolimus + lansoprazole

MPA, mycophenolic acid; MMF, mycophenolate mofetil; PPI, proton pump inhibitor; $C_{\text{max}}$, maximum concentration

Miura M et al. Ther Drug Monit 2008;30:46–51
Proton pump inhibitors interfere with the immunosuppressive potency of mycophenolate mofetil

Matthias Schaier¹, Christian Scholl¹, Dominik Scharpf¹, Friederike Hug¹, Sabine Bönisch-Schmidt¹, Ralf Dikow¹, Wilhelm H. Schmitt², Vedat Schwenger¹, Martin Zeier¹ and Claudia Sommerer¹
Schaier M et al. Rheumatology 2010;49:2061–2067
PPI co-medication and potential implications for MPA dosing and outcomes

- Use of PPIs in transplant recipients

- **PPIs and the consequences for MPA AUC**
  - With MMF
  - With EC-MPS

- MPA AUC and efficacy

- Efficacy of EC-MPS vs MMF

PPI, proton pump inhibitor; MPA, mycophenolic acid; AUC, area under the concentration-time curve; MMF, mycophenolate mofetil; EC-MPS, enteric-coated mycophenolate sodium
EC-MPS-derived MPA absorption is dependent on intestinal pH

EC-MPS is absorbed in the intestine at pH >5.5

EC-MPS contains the active ingredient as the sodium salt of MPA

MPA release from EC-MPS occurs at pH >5.5

Solubility (%)

pH-dependent release of MPA from the EC-MPS 360 mg tablet

MMF, mycophenolate mofetil; MPA, mycophenolic acid; EC-MPS, enteric-coated mycophenolate sodium

### MPA exposure (AUC) is similar with EC-MPS or MMF

Randomised, crossover, single-dose study in 24 stable renal transplant patients

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>EC-MPS 720 mg</th>
<th>MMF 1000 mg</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median $t_{\text{max}}$, h</td>
<td>24</td>
<td>2.0</td>
<td>0.75</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean AUC$_{0-\infty}$, $\mu$g.h/mL</td>
<td>24</td>
<td>66.5</td>
<td>63.7</td>
<td>ns</td>
</tr>
</tbody>
</table>

MPA, mycophenolic acid; AUC, area under the concentration-time curve; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; $t_{\text{max}}$, time to maximum concentration; ns, not significant

MPA exposure is not influenced by concomitant PPI and EC-MPS treatment\textsuperscript{a} in healthy volunteers

\textsuperscript{a}Following a single oral dose of MMF 1000 mg or EC-MPS 769 mg (equivalent to 720 mg MPA)
MPA, mycophenolic acid; PPI, proton pump inhibitor;
EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil

Co-administration of a PPI decreases MPA exposure with MMF but not EC-MPS

2 crossover studies in healthy volunteers: Study 1, MMF 1000 mg + pantoprazole vs MMF (n=12); Study 2, EC-MPS 720 mg + pantoprazole vs EC-MPS (n=12)

* 27%*  
* 57%*  

*p<0.05  
PPI, proton pump inhibitor; MPA, mycophenolic acid; MMF, mycophenolate mofetil; EC-MPS, enteric-coated mycophenolate sodium; AUC, area under the concentration-time curve; C_{max}, maximum concentration

PPI co-medication and potential implications for MPA dosing and outcomes

- Use of PPIs in transplant recipients
- PPIs and the consequences for MPA AUC
  - With MMF
  - With EC-MPS
- MPA AUC and efficacy
- Efficacy of EC-MPS vs MMF

PPI, proton pump inhibitor; MPA, mycophenolic acid; AUC, area under the concentration-time curve; MMF, mycophenolate mofetil; EC-MPS, enteric-coated mycophenolate sodium
Concentration-controlled MPA exposure is associated with improved efficacy

Incidence of BPAR was significantly lower in the CC compared with the FD group (7.7% vs 24.6%; p=0.01)

In the CC group, MMF dose adjustments were calculated to reach an MPA AUC target of 40 mg h/L

CC, concentration controlled; MPA, mycophenolic acid; FD, fixed dose; BPAR, biopsy-proven acute rejection

Higher MPA exposure early post-transplant is associated with lower BPAR risk

- MPA AUC at later time points (Day 10, Month 1) did not significantly correlate with BPAR (p=0.2572, p=0.5588)
- During 1st year post-transplant, risk of BPAR decreased with increasing MPA AUC (–0.0222 [95% CI –0.0288, –0.0016]; p=0.0247)

MPA, mycophenolic acid; BPAR, biopsy-proven acute rejection; AUC, area under the concentration-time curve; CI, confidence interval

In a retrospective study, EC-MPS was associated with higher mean MPA dose than MMF

1709 consecutive renal transplant patients (2000–2006) from a single centre

<table>
<thead>
<tr>
<th>Time following initiation of MPA therapy</th>
<th>Mean equimolar-adjusted MPA dose (mg)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>MMF (n=1111): 1174</td>
<td>EC-MPS (n=598): 1257</td>
</tr>
<tr>
<td>1 year</td>
<td>MMF (n=1111): 1136</td>
<td>EC-MPS (n=598): 1232</td>
</tr>
<tr>
<td>2 years</td>
<td>MMF (n=1111): 1108</td>
<td>EC-MPS (n=598): 1189</td>
</tr>
</tbody>
</table>

EC-MPS, enteric-coated mycophenolate sodium; MPA, mycophenolic acid; MMF, mycophenolate mofetil

Sollinger HW et al. Transplantation 2010;89:446–51
PPI co-medication and potential implications for MPA dosing and outcomes

- Use of PPIs in transplant recipients
- PPIs and the consequences for MPA AUC
  - With MMF
  - With EC-MPS
- MPA AUC and efficacy
- Efficacy of EC-MPS vs MMF

PPI, proton pump inhibitor; MPA, mycophenolic acid; AUC, area under the concentration-time curve; MMF, mycophenolate mofetil; EC-MPS, enteric-coated mycophenolate sodium
Lower rate of BPAR with EC-MPS vs MMF: 2-centre retrospective analysis


*Significant difference despite similar incidence of GI adverse events and dose manipulations
Having a dose manipulation was strongly associated with BPAR regardless of product used (hazard ratio 4.366; 95% CI 2.222, 8.578; p<0.001)

BPAR, biopsy-proven acute rejection; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; GI, gastrointestinal; CI, confidence interval

Cooper M et al. Transplantation 2009;88:514–20
Lower incidence of BPAR with EC-MPS vs MMF: single-centre retrospective analysis

1709 consecutive renal transplant patients (2000–2006) from a single centre

Graft survival

Acute kidney rejection

BPAR

Percentages based on 2-year Kaplan-Meier estimates; p values based on a log-rank test

BPAR, biopsy-proven acute rejection; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; ns, not significant

Sollinger HW et al. Transplantation 2010;89:446–51
Lower incidence of BPAR with EC-MPS vs MMF: pooled analysis

Pooled analysis of de novo kidney transplant patients receiving EC-MPS or MMF with CsA and steroids in 4 multicentre studies

- Death, graft loss or BPAR
  - MMF (n=602): 28.9%
  - EC-MPS (n=1289): 24.4%

- BPAR
  - MMF: 20.2%
  - EC-MPS: 23.9%

- Graft loss
  - MMF: 6.1%
  - EC-MPS: 3.5%

- Death
  - MMF: 2.3%
  - EC-MPS: 1.2%

BPAR, biopsy-proven acute rejection; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; CsA, cyclosporin

Salvadori M et al. Transplant Proc 2010;42:1325–8
Lower incidence of BPAR with MMF vs EC-MPS: retrospective analysis

Retrospective database analysis of de novo kidney transplant patients receiving EC-MPS or MMF maintenance IS at the time of discharge (UNOS/OPTN Registry)

Incidence at 3 years (%)
Conclusions

- PPIs are commonly used in treatment of transplant recipients\(^1\) but their effect on pH influences the solubility and hydrolysis of MMF\(^2,3\)

- Co-administration of PPI and MMF reduces MPA exposure,\(^4\)–\(^6\) which may compromise efficacy\(^7,8\)

- EC-MPS delays MPA release until the small intestine,\(^9\) resulting in a higher MPA exposure than MMF\(^6,9,10\)

- Data suggest that EC-MPS is associated with improved efficacy over MMF\(^10\)–\(^12\)

PPI, proton pump inhibitor; MMF, mycophenolate mofetil; MPA, mycophenolic acid; EC-MPS, enteric-coated mycophenolate sodium

Sotrastaurin
Current Immunosuppressants
Points of Therapeutic Intervention

Rejection

Graft

Effector T Cells

Lymph node

Graft DC – host T cell interaction, leading to T cell activation

T Cell proliferation, leading to clonal expansion

Azathioprine (purine antagonist)
Sirolimus, Everolimus (mTOR)
Mycophenolate (IMPDH)
Basiliximab (CD25)

CsA, Tacrolimus (CN)

CN: calcineurin; PKC: protein kinase C; IMPDH: Inosine monophosphate dehydrogenase
Current Immunosuppressants
Points of Therapeutic Intervention

Rejection

Graft DC – host T cell interaction, leading to T cell activation

CsA, Tacrolimus (CN)

Sotrastaurin (PKC)

Lymph node

Effector T Cells

T Cell proliferation, leading to clonal expansion

Azathioprine (purine antagonist)
Sirolimus, Everolimus (mTOR)
Mycophenolate (IMPDH)
Basiliximab (CD25)

CN: calcineurin; PKC: protein kinase C; IMPDH: Inosine monophosphate dehydrogenase
Sotrastaurin (STN): Mechanism of action

Protein kinase C (PKC): A novel target in transplantation

STN is a small molecular weight immuno-suppressant with a novel mode of action:

- PKCs are known to integrate signals which emanate from the T cell antigen receptor (TCR) and the CD28 co-receptor and which together lead to T cell activation.
- STN potently and selectively inhibits all classical & novel PKC isozymes.
- Like CNIs, STN inhibits T cell activation but through inhibition of a different target, i.e., PKCs.
- Mode of action different from CNIs, and complementary to CNIs.

Potential for CNI replacement, or for allowing CNI-minimisation when combined with CNI.
Phase II program in kidney transplantation

- A2207 – STN + myfortic from transplantation final analysis available
- A2203 – STN + Tac, converted to STN + myfortic final analysis available
- A2206 – STN + Certican from transplantation study ongoing
- A2214 – STN + Tac dose-ranging: study ongoing

Simulect and steroids were used in all studies, across all study arms
Phase II program in kidney transplantation

- A2207 – STN + myfortic from transplantation
  final results available

- A2203 – STN + Tac, converted to STN + myfortic
  final results available

- A2206 – STN + Certican from transplantation
  study ongoing

- A2214 – STN + Tac dose-ranging: starting soon
A2207 study design
*CNIm-free STN + myfortic regimen from transplantation*

12 months treatment

Screening

- Basiliximab, 20mg + MPA, 720mg

Randomization (2:1)

- Tacrolimus + MPA + Steroids
  - N = 44

- STN (300mg bid) + MPA + Steroids
  - N = 81
Efficacy results

*Kaplan–Meier plot of time to first on-treatment composite efficacy failure*

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Control</th>
<th>STN + MPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.5%</td>
<td>34.7%</td>
</tr>
<tr>
<td>30</td>
<td>25.7%</td>
<td>34.7%</td>
</tr>
<tr>
<td>60</td>
<td>4.5%</td>
<td>25.7%</td>
</tr>
</tbody>
</table>

Proportion of Patients Free from Event

Study Day
Estimated GFR higher on the STN-myfortic regimen

All patients, including also those who didn’t remain on study therapy

Median GFR by MDRD by treatment

<table>
<thead>
<tr>
<th>Days on treatment</th>
<th>Control</th>
<th>STN+MPA</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>41</td>
<td>77</td>
<td>0.084</td>
</tr>
<tr>
<td>14</td>
<td>39</td>
<td>69</td>
<td>0.002</td>
</tr>
<tr>
<td>21</td>
<td>39</td>
<td>69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30</td>
<td>42</td>
<td>67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>60</td>
<td>37</td>
<td>61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>90</td>
<td>36</td>
<td>60</td>
<td>0.006</td>
</tr>
</tbody>
</table>

N providing data:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>77</th>
<th>69</th>
<th>69</th>
<th>67</th>
<th>61</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>STN+MPA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>41</td>
<td>39</td>
<td>39</td>
<td>42</td>
<td>37</td>
<td>36</td>
</tr>
</tbody>
</table>
## Safety: Adverse events (1/2)

(≥10% in any group and a difference of ≥5% between sotrastaurin and controls)

|                | Tac + MPA  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=44</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (32%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (23%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (18%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

|                | STN + MPA  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=81</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33 (41%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>46 (59%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>35 (43%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25 (31%)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>11 (14%)</td>
</tr>
</tbody>
</table>

- Higher heart rate in STN+MPA group (~8–10 bpm) without evidence of being pro-arrhythmic or of increased risk of an ischemic event
- Higher rates of diarrhea, constipation, nausea, and vomiting compared with control, but successfully managed with standard methods
- Dysgeusia in STN+MPA group only; not causing discontinuation
### Safety: Adverse events (2/2)

(≥10% in any group and a difference of ≥5% between sotrastaurin and controls)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Tac + MPA</th>
<th>STN + MPA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=44</td>
<td>N=81</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (14%)</td>
<td>16 (20%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>9 (21%)</td>
<td>12 (15%)</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>8 (18%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>6 (14%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>9 (21%)</td>
<td>12 (15%)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>11 (25%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5 (11%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (16%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Tremor</td>
<td>9 (21%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7 (16%)</td>
<td>21 (26%)</td>
</tr>
</tbody>
</table>

- Lower incidence of headache, tremor, or electrolyte disorders in STN+MPA
Phase II program in kidney transplantation

- A2207 – STN + myfortic from transplantation final results available
- A2203 – STN + Tac, converted to STN + myfortic final results available
- A2206 – STN + Certican from transplantation study ongoing
- A2214 – STN + Tac dose-ranging: study ongoing
A2203 – study design (1/2)

Starting regimen STN 200mg bid + tacrolimus (standard or reduced)

- Phase II, multicentre, open-label, randomized study
- 28 centers in Europe and North America

Renal Tx

Day 0

Randomization
1:1:1

Basiliximab

<24 h

Day 4

Control;
Tac target 8-15 (M1), 6-12 (M2-3), 5-10 (≥ M4)

STN+standTac;
Tac target 8-15 (M1), 6-12 (M2-3)

STN+redTac;
Tac target 5-8 (M1), 3-6 (M2-3)

CONVERSION
Month 3

Initial comparator: MPA
A2203 – study design (2/2)

After month 3, conversion to a CNI-free STN + MPA regimen

- Phase II, multicentre, open-label, randomized study
- 28 centers in Europe and North America

**Randomization**  
1:1:1

**CONVERSION**  
Month 3  
Analysis of Composite Efficacy

Month 6  
Primary Endpoints

Month 12  
Study end

Renal Tx  
Day 0  
Basiliximab

Day 4  
Basiliximab

<24 h

MPA (720 mg, bid)+standTac  (N=74)

STN (200 mg, bid)+standTac  (N=76)

STN (200 mg, bid)+redTac  (N=66)

STN (200 mg, bid)+MPA (720 mg, bid)

STN (200 mg, bid)+MPA (720 mg, bid)

after 3 months: comparator tacrolimus (standard exposure)
Actual achieved tacrolimus trough levels

**Tacrolimus withdrawn in STN+Tac arms Months 3-4**

- **Control**: Tac target 8-15 (M1), 6-12 (M2-3), 5-10 (≥ M4)
- **STN+standTac**: Tac target 8-15 (M1), 6-12 (M2-3)
- **STN+redTac**: Tac target 5-8 (M1), 3-6 (M2-3)

<table>
<thead>
<tr>
<th>N providing data</th>
<th>Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>62</td>
</tr>
<tr>
<td>STN+standTac</td>
<td>60</td>
</tr>
<tr>
<td>STN+redTac</td>
<td>56</td>
</tr>
</tbody>
</table>
Excellent efficacy of the STN+standTac and STN+redTac regimens during the first 3 months

Control  74  60
STN+standTac  76  63
STN+redTac  66  56
Excellent efficacy of the STN+standTac and STN+redTac regimens during the first 3 months

Incidence of biopsy-proven acute rejections up to day 90:
Tac + MPA: 2 / 74 (3%)
STN + standTac: 3 / 76 (4%)
STN + redTac: 2 / 66 (3%)

N with data:
- Control: 74, 60
- STN+standTac: 76, 63
- STN+redTac: 66, 56
Excellent efficacy of the STN+standTac and STN+redTac regimens during the first 3 months, not maintained on STN+MPA regimen.
Renal function: No between-treatment difference in GFR (MDRD) Safety population

GFR: glomerular filtration rate
Sotrastaurin $C_0$ levels unaffected by tacrolimus or MPA

Kovarik et al et al; Transplantation 2011;91: 317–322
Tacrolimus exposure is significantly increased by sotrastaurin in the initial weeks posttransplant by a pharmacokinetic interaction.

Kovarik et al et al; Transplantation 2011;91: 317–322

Mean tacrolimus predose drug concentrations (C0)

Mean dose-normalized tacrolimus C0

A  Standard tacrolimus exposure with mycophenolic acid
B  Sotrastaurin 200 mg bid + Tacrolimus standard exposure
C  Sotrastaurin 200 mg bid + Tacrolimus reduced exposure
Safety: Adverse events more frequent on STN
(*≥10% in any group and a difference of ≥5% between sotrastaurin and controls*)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Tac + MPA N=74</th>
<th>STN + standTac N=75</th>
<th>STN + redTac N=66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocalcemia</td>
<td>3%</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>22%</td>
<td>31%</td>
<td>25%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1%</td>
<td>16%</td>
<td>19%</td>
</tr>
<tr>
<td>Constipation</td>
<td>26%</td>
<td>37%</td>
<td>32%</td>
</tr>
<tr>
<td>Nausea</td>
<td>26%</td>
<td>35%</td>
<td>28%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16%</td>
<td>20%</td>
<td>28%</td>
</tr>
<tr>
<td>Headache</td>
<td>10%</td>
<td>19%</td>
<td>17%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3%</td>
<td>4%</td>
<td>11%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>5%</td>
<td>13%</td>
<td>8%</td>
</tr>
</tbody>
</table>
Safety: Adverse events less frequent on STN
(≥10% in any group and a difference of ≥5% between sotrastaurin and controls)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Tac + MPA N=74</th>
<th>STN + standTac N=75</th>
<th>STN + redTac N=66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>14%</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>16%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>51%</td>
<td>41%</td>
<td>39%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>14%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Back pain</td>
<td>12%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Tremor</td>
<td>24%</td>
<td>15%</td>
<td>22%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>22%</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15%</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>39%</td>
<td>31%</td>
<td>25%</td>
</tr>
</tbody>
</table>
A2203, conclusions

- STN + tacrolimus showed excellent efficacy in renal transplant recipients; however, the post-conversion STN + MPA regimen was inferior to the control.

- Both STN regimens were generally well tolerated; no difference versus control regarding:
  - Renal function
  - Overall incidences of GI AEs
  - Infection incidence

- Less effect on leukocytes/neutrophils for STN + tacrolimus regimens used up to month 3 than for MPA + tacrolimus.

- STN + tacrolimus deserves further dose-ranging and longer-term assessment (beyond 3 months).
Phase II program in kidney transplantation

- A2207 – STN + myfortic from transplantation
  final results available

- A2203 – STN + Tac, converted to STN + myfortic
  final results available

- A2206 – STN + Certican from transplantation
  study ongoing

- A2214 – STN + Tac dose-ranging: just started
Study A2206: design and status

- Study A2206

- Design: 2-arm (2:1 randomization), open-label
  Simulect + steroids for all patients

- Stage 1 (recruited in 2007/2008):
  - STN 300mg bid + Certican®
  - Neoral low exposure + Certican®

3-month results of stage 1 (Q1’09) were used to decide on appropriate dose ranging for Stage 2, which is currently ongoing
### Sotrastaurin and everolimus pharmacokinetics after single-dose coadministration


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug alone</th>
<th>Drug combination</th>
<th>Ratio (90%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sotrastaurin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( t_{\text{max}} ) (h)</td>
<td>1 (0.5 – 3)</td>
<td>2 (0.5 – 4)</td>
<td>–</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>638 ± 295</td>
<td>539 ± 211</td>
<td>0.87 (0.76, 1.00)</td>
</tr>
<tr>
<td>( \text{AUC}_{\text{inf}} ) (ng \times h/ml)</td>
<td>3660 ± 1853</td>
<td>3630 ± 2006</td>
<td>1.00 (0.88, 1.13)</td>
</tr>
<tr>
<td>( t_{1/2} ) (h)</td>
<td>5.9 ± 1.1</td>
<td>6.2 ± 1.5</td>
<td>–</td>
</tr>
<tr>
<td><strong>N-desmethyl-sotrastaurin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( t_{\text{max}} ) (h)</td>
<td>1 (0.5 – 3)</td>
<td>2.5 (1 – 4)</td>
<td>–</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>22 ± 10</td>
<td>19 ± 8</td>
<td>0.85 (0.75, 0.97)</td>
</tr>
<tr>
<td>( \text{AUC}_{0-t} ) (ng \times h/ml)</td>
<td>125 ± 41</td>
<td>120 ± 44</td>
<td>0.99 (0.87, 1.13)</td>
</tr>
<tr>
<td>Metabolic ratio</td>
<td>0.030 ± 0.009</td>
<td>0.030 ± 0.008</td>
<td>–</td>
</tr>
<tr>
<td><strong>Everolimus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( t_{\text{max}} ) (h)</td>
<td>1 (0.5 – 1)</td>
<td>1 (0.5 – 1)</td>
<td>–</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>15 ± 6</td>
<td>16 ± 6</td>
<td>1.15 (0.99, 1.33)</td>
</tr>
<tr>
<td>( \text{AUC}_{\text{inf}} ) (ng \times h/ml)</td>
<td>114 ± 50</td>
<td>137 ± 56</td>
<td>1.20 (1.05, 1.37)</td>
</tr>
<tr>
<td>( t_{1/2} ) (h)</td>
<td>39 ± 6</td>
<td>40 ± 7</td>
<td>–</td>
</tr>
</tbody>
</table>

**Everolimus AUC is 20% increased by sotrastaurin**  
**Sotrastaurin exposure is not altered by everolimus**
Phase II program in kidney transplantation

- A2207 – STN + myfortic from transplantation final results available
- A2203 – STN + Tac, converted to STN + myfortic final results available
- A2206 – STN + Certican from transplantation study ongoing

- A2214 – STN + Tac dose-ranging: study ongoing
  - STN + further reduction of tacrolimus
  - Lower STN dose with tacrolimus
A2214 – study design

Dose ranging STN 100, 200 or 300 mg bid + tacrolimus

- Phase II, multicentre, double-blind, randomized study
- Europe, Latin and North America, Asia (Korea), Australia

Comparator: MPA (myfortic)
Summary and Conclusions

- Sotrastaurin is a novel first-in-class PKC inhibitor being developed for transplantation and autoimmune diseases
- Overall favorable safety profile, with gastrointestinal AEs comparable to standard treatments and no evidence of renal, hematological or metabolic toxicity
- STN + mycophenolate not meeting efficacy needs, will not be pursued in renal transplantation with current formulation
- STN + tacrolimus showed excellent efficacy in renal transplant recipients; however, the post-conversion STN + MPA regimen was inferior to the control
- STN + Everolimus: study ongoing
- Future studies will investigate CNI-free and “ultra low CNI exposure” regimens