MP039

# THE EFFECT OF EVEROLIMUS IN PATIENTS WITH RENAL ANGIOMYOLIPOMA ASSOCIATED WITH TUBEROUS SCLEROSIS COMPLEX

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## INTRODUCTION

- Tuberous sclerosis complex (TSC) is a genetic disorder caused by TSC1/TSC2 mutations, which trigger mammalian target of rapamycin (mTOR) activation and undercontrolled cellular proliferation[1]. The disease is characterized by growth of non-malignant tumours, including renal angiomyolipomas (AML) in up to 80% of patients[2].
- Renal AML are tumours whose progressive enlargement may increase the risk of haemorrhages and encroach renal parenchyma[3]. Preserving kidney function and preventing haemorrhages are therefore the main goals of AML treatment, which has mainly included surgical procedures or embolization.
- The mTOR inhibitor everolimus has arisen as a non-surgical treatment alternative for TSC-related renal AMLs. Its administration over the EXIST-2 trial supported everolimus efficacy for these tumours[4,5], with a manageable safety profile consistent with previous reports on other TSC populations[6,7]. This positive benefit/risk balance was the basis for requesting the European Medicines Agency's authorization for this indication.

## OBJECTIVE

- We conducted this trial to provide further knowledge on the effect of everolimus in patients with TSC-related renal AMLs under real practise conditions.

## METHODS

### Study design

- This was a Spanish, open-label, single-arm, phase IIIb, expanded access trial.

### Patient population

- The study included adult patients with TSC-related renal AML **(Figure 1)**.

**Figure 1.** Main selection criteria

| Main inclusion criteria | Main exclusion criteria |
|---|---|
| • Patients aged ≥18 years<br>• At least one renal AML of ≥3 cm in its longest diameter as per CT or MRI<br>• Definite diagnosis of TSC according to the modified Gomez criteria* | • AML requiring surgery<br>• AML-related bleeding/embolisation within the previous 6 months<br>• Prior heart attack, angina pectoris, hemorrhagic stroke related to atherosclerosis, impaired lung functioning, organ transplantation, or surgery within the previous 2 months<br>• Presence of the following conditions: significant haematological/hepatic abnormality, serum creatinine >1.5 times the ULN, haemorrhagic diathesis, treatment with vitamin K antagonist, uncontrolled hyperlipidaemia/diabetes, uncontrolled/severe disease, or ongoing/active infection (except for hepatitis B/C virus) |

Abbreviations: AML, angiomyolipoma; CT, computed tomography; MRI, magnetic resonance imaging; TSC, tuberous sclerosis complex; ULN, upper limit of normal. *Roach et al. J Child Neurol. 1998;13:624-8; Hyman et Whittemore. Arch Neurol. 2000;57:662-5.

### Study treatment and assessments

- Everolimus was initiated at 10 mg once daily, adjusted on the basis of safety findings, and prolonged until disease progression, unacceptable toxicity, patient's death/withdrawal, or one year after first patient enrolment **(Figure 2)**.

**Figure 2.** Study flow chart

| Screening/baseline assessments (≤21 days pre-treatment) | Everolimus administration (until disease progression, unacceptable toxicity, patient's death/withdrawal, or one year after first patient enrolment) | Post-treatment safety follow-up (28 days post-treatment) |
|---|---|---|
| • Informed consent<br>• Selection criteria<br>• Demographics<br>• Medical history<br>• Comorbidities<br>• Clinical examination<br>• Laboratory analyses<br>• Kidney CT/MRI<br>• Concomitant medication | • Study treatment administration<br>• Clinical examination<br>• Laboratory analyses<br>• Kidney CT/MRI (months 3, 6, 12/end of treatment)<br>• Concomitant medication<br>• Adverse events | • Concomitant medication<br>• Adverse events |

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

- Radiologic AML response was assessed on CT/MRI scans at months 3, 6, and 12/end of treatment:
  - *Radiologic response:* ≥50% reduction in the sum of volumes of AML target lesions, confirmed in a second scan (approximately 12 weeks later), and absence of new lesions ≥1cm, kidney volume increase >20%, and AML-related grade ≥2 bleeding or need for embolisation/surgery.
  - *Radiologic progression:* ≥25% increase in the sum of volumes of AML target lesions and/or ≥20% increase in the volume of either kidney, new lesions ≥1cm, and/or AML-related grade ≥2 bleeding or need for embolisation/surgery.

## RESULTS

### Patient characteristics

- Between May 2013 and May 2014, 19 patients were included **(Table 1)**.

**Table 1.** Baseline patient characteristics (N=19)

| Characteristics | Value |
|---|---|
| **Median age,** years (IQR) | 38.0 (29.0-43.0) |
| **Gender,** n (%) | |
| Female | 13 (68.4) |
| Male | 6 (31.6) |
| **Race,** n (%) | |
| White | 19 (100) |
| **Median volume of renal AML lesions,** ml (IQR) | 260.0 (127.8-322.2) |
| **Median volume of right kidney,** ml (IQR) | 278.0 (184.8-809.6)* |
| **Median volume of left kidney,** ml (IQR) | 275.5 (173.4-402.4)* |

*Abbreviations: AML, angiomyolipoma; IQR, interquartile range.*
**N=18, as one patient had previously undergone nephrectomy.*

### Study treatment administration

- Everolimus was administered for a median of 6.6 (5.3-10.9) months **(Table 2)**.

**Table 2.** Everolimus administration (N=19)

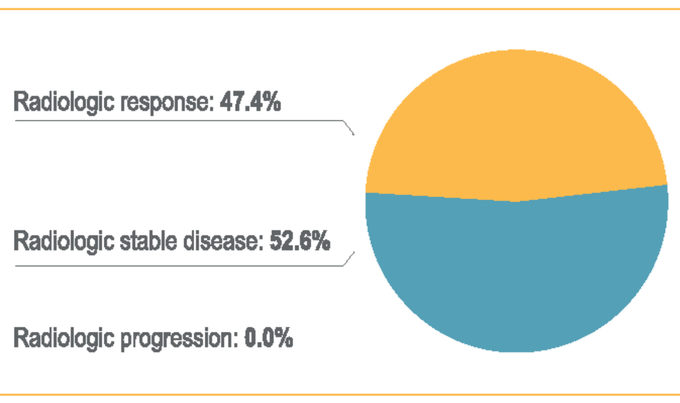
| Characteristics | Value |
|---|---|
| **Median everolimus exposure,** months (IQR) | 6.6 (5.3-10.9) |
| **Dose of 10 mg/day over the whole study,** n (%) | 11 (57.9) |
| **Dose reduction/interruption due to adverse events,** n (%) | 8 (42.1) |
| **Treatment discontinuation,** n (%) | 0 (0.0) |

*Abbreviations: IQR, interquartile range.*

### Efficacy

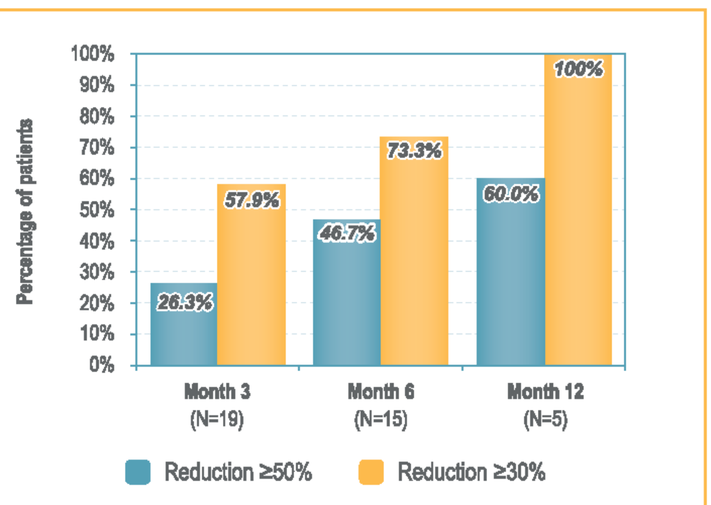
- Nine (47.4%) patients showed radiologic response of renal AML, after a median of 3.3 (3.0-6.2) months from everolimus initiation; none progressed **(Figure 3)**.

**Figure 3.** Radiologic angiomyolipoma response (N=19)




- AML reduction from baseline ≥30% was observed in 11 (57.9%) patients and ≥50% in 9 (47.4%) patients. Reductions in each study visit are summarized in **Figure 4**.

**Figure 4.** Reductions in renal angiomiolipoma volume in each study visit



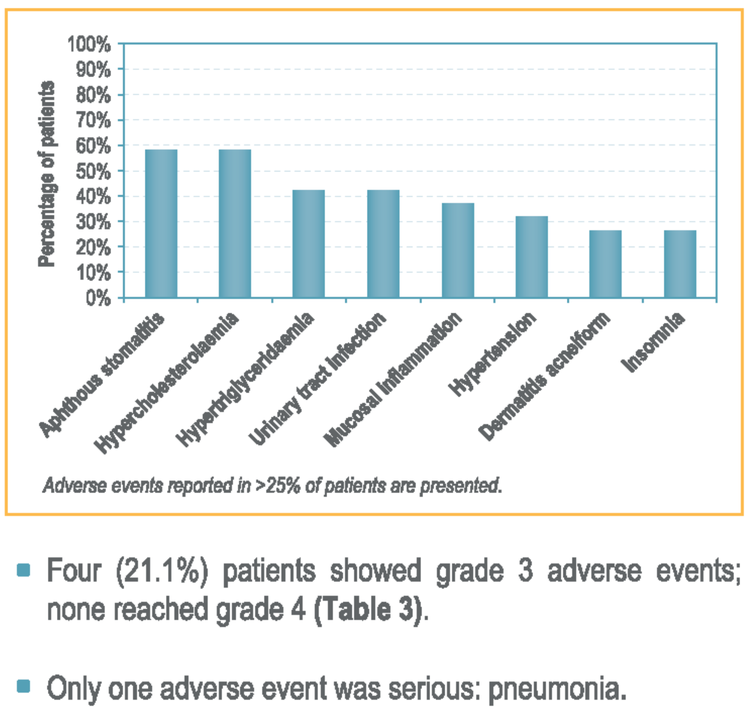

*The study ended as per protocol one year after first patient enrolment, which explains the reduced number of patients available at month 12.*

- Right and left kidney volumes decreased in 17 (94.4%) and 14 (87.5%) patients, respectively.

### Safety

- Adverse events most frequently included aphthous stomatitis, hypercholesterolaemia, hypertriglyceridaemia, and urinary tract infection **(Figure 5)**.

**Figure 5.** Most frequent adverse events (N=19)




*Adverse events reported in >25% of patients are presented.*

- Four (21.1%) patients showed grade 3 adverse events; none reached grade 4 **(Table 3)**.
- Only one adverse event was serious: pneumonia.

**Table 3.** Grade 3/4 adverse events (N=19)

| Adverse events | n (%) |
|---|---|
| **Grade 3 adverse events** | 4 (21.1) |
| Hypertriglyceridaemia | 2 (10.5) |
| Transaminases increased | 1 (5.3) |
| Hypertension | 1 (5.3) |
| Mucosal inflammation | 1 (5.3) |
| **Grade 4 adverse events** | 0 (0.0) |

## CONCLUSIONS

- The study findings support the efficacy of everolimus in reducing TSC-related renal AML lesions and overall kidney volumes, with evident benefits just a few months after starting the treatment.
- These benefits were accompanied by a manageable safety profile that did not raise new safety concerns.
- Everolimus may therefore contribute to improve the management of TSC-related renal AML in clinical practice.

## References

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