

## Supplementary information. Patient selection and primary outcome measurements

### **Patient selection**

#### **Inclusion criteria**

a: Moderate-to-severe Graves' orbitopathy (GO), defined by having at least one of the following signs: moderate or severe soft tissue swelling; inconstant or constant diplopia in primary position; proptosis of 18 mm or more (the normal range of proptosis for Chinese is 12~15 mm, according to EUGOGO statement, moderate-to-severe was considered when exophthalmos  $\geq 3$  mm above normal range for race);

b: Active GO: Patients presenting with a CAS of three points or more;

c: Euthyroidism as indicated by normal range of free thyroxine (FT4, 9-23 pmol/l) and free tri-iodothyronine (FT3, 3.5-6.8 pmol/l) and thyrotropin concentration within or below the reference range (TSH, 0.35-5.0 mU/L). Euthyroidism can be rendered by antithyroid drugs or following thyroidectomy, or 6 months following <sup>131</sup>Iodine administration;

d: Patients not receiving treatments (radiotherapy, glucocorticoids, immunosuppressive agents or surgery) for their orbitopathy except for local measures.

e: Age 18-60 years.

### **Exclusion criteria**

a: CAS < 3/7;

b: Mild GO;

c: Sight-threatening GO (including corneal breakdown and/or dysthyroid optic neuropathy).

Dysthyroid optic neuropathy (DON) was considered if there was disc swelling/pallor, visual field defect, and/or best corrected visual acuity (BCVA) less than 20/30 in absence of other reasons for sign loss;

d: Patients with diabetes mellitus or other severe concomitant illness;

e: Women with pregnancy or breast-feeding their children;

f: Contraindications to the use of doxycycline.

### **Primary outcome measurements**

Overall treatment response was graded as: improvement, deterioration, and no success.

a: Improvement, when at least one major criteria or two minor criteria were achieved, in absence of deterioration of any criterion in that observed eye. Three major criteria were: improvement in diplopia grade (disappearance or change in grade); improvement of  $\geq 8$  degrees in any direction of eye movements; reduction of three points or more in CAS. Four minor criteria were: reduction of 2 mm or more in eyelid aperture; reduction of 2 mm or

more in proptosis; improvement in grade of soft tissue swelling; decrease in CAS by at least two points.

b: Deterioration, defined as occurrence of DON, and/or worsening of soft tissue swelling, and/or worsening of diplopia, and/or an increase of  $\geq 2$  mm in lid aperture, and/or an increase of  $\geq 2$  mm in proptosis, and/or a decrease of  $\geq 8$  degrees in duction.

c: No success was defined if there was no change or the changes did not reach the improvement criteria.