Hereditary angioedema (HAE) is due to C1 esterase inhibitor deficiency (Types 1 or 2) but also occurs in patients with normal C1 esterase inhibitor. HAE with normal inhibitor has been linked with mutations in genes for Factor XII, plasminogen and angiopoietin but the underlying mutation in other patients is unknown. The HELP-03 study population was drawn from patients with Type 1 or Type 2 HAE so the analysis and implementation of the technology appraisal should be confined to HAE types 1 and 2 and clearly stated as such.

HAE presents with angioedema without weals. Angioedema without weals may also be a presentation of chronic spontaneous urticaria (CSU). CSU is considerably more common than HAE but angioedema probably never results in asphyxiation and can be expected to remit naturally whereas HAE may cause death from asphyxiation in a few individuals1 and is potentially life long.

The aim of treatment of HAE should be complete disease control to prevent a risk of asphyxiation and improve quality of life.

The only licensed treatment for long-term prophylaxis of patients 6 years and older with HAE types 1 and 2 in the UK is Cinryze (C1 esterase inhibitor) by intravenous administration. Berinert (C1 esterase inhibitor) is licensed for treatment and pre-procedure prevention of acute attacks of HAE but not for long-term prophylaxis even though it is commonly used off licence for this. The correct financial comparator for lanadelumab should therefore be Cinryze rather than Berinert, despite estimated lower NHS usage (section 3.12).

Self-administration by subcutaneous injection is much easier for patients than repeated intravenous cannulation and safer in the context of poor peripheral access requiring long-term central lines. The subcutaneous route is likely to be an increasing advantage over a lifetime as venous access becomes more difficult and the ability of patients to self-cannulate becomes less with age.

As a further confounder, in the calculation of cost, it should not be forgotten that acute breakthrough episodes still require emergency treatment with C1 inhibitor (Berinert, Cinryze or Ruconest) or icatibant +/- supportive medical care so the total costs to the NHS of lanadelumab will not be limited to prophylactic administration. Furthermore, the need for high frequency administration may be
reduced by co-administration of oral prophylaxis (danazol or tranexamic) where tolerated and appropriate. The HELP-03 study provides no data to estimate any advantage of concurrent oral treatment in terms of attack frequency, severity or optimal treatment frequency.

Concentrated C1 esterase inhibitor (Haegarda™) by subcutaneous injection has recently been approved by the FDA for long-term prophylaxis based presumably on data from the COMPACT trial. Guidance on using lanadelumab in the NHS in England should be revisited if EMA approval for its use in Europe is granted or pending.