

**Berotrastat for the prophylaxis of hereditary angioedema –  
Real World Evidence data from the United Kingdom**

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Original Article Topics:	Autoimmunity and Clinical Immunology
News and Views Topics:	
Keywords:	angioedema, clinical immunology, quality-of-life

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Abstract:	

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Manuscripts

## Point-by-point response

**Date:** 12/11/2022

**Manuscript Number:** ALL-2022-00604

**Title of Article:**

Berotrastat for the prophylaxis of hereditary angioedema – Outcomes in the United Kingdom

**Name of the Corresponding Author:** Dr Manisha Ahuja

**Email Address of the Corresponding Author:** Manisha.ahuja1@nhs.net

Dear María José Torres and Cezmi Akdis,

I am very grateful to the reviewers for taking the time to make further comments on the revised manuscript. I have replied to each comment below and hope that the answers are satisfactory.

This work represents the largest body of real-world experience available in using Berotrastat for the prophylaxis of hereditary angioedema. We have found this work extremely valuable for guiding further discussions in national forums within the UK and during discussions in EAACI. We hope that this data is useful for clinicians worldwide who are trying to achieve the best possible care for their patients with hereditary angioedema.

**Major changes and additions to the revised manuscript (please list):**

1. Data comparison between our project and previous clinical trials has now been restructured as suggested. The manuscript now contains our data in the main body of the text, with comparisons noted in the concluding paragraph.

**Specific Responses:**

**Response to Reviewer #2**

**Comment 1:** Authors revised and modified the manuscript according to the suggestions and criticisms. I feel that it is important to publish the RWE data supporting the data from the clinical trials. I have some minor comments listed below. In the title of the paper I would recommend to change "Outcome in the United Kingdom" to "RWE data from the United Kingdom"

**Reply 1:** Thank you, we agree this is a better title and I have made this change in the manuscript.

1  
2  
3 **Comment 2:** Since there are some discrepancies compared to the results from clinical trials, I  
4 would recommend to add 2-3 sentences at the end of the manuscript stating and comparing  
5 the observed results with the data from trials - e.g. the effectiveness was comparable, the  
6 tolerability was...etc. In this version, there are only statements about the data from this  
7 observation and from the clinical trials without comparison.  
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10 **Reply 2:** Thank you. The data collected through our project doesn't directly compare with the  
11 clinical trials and so it can be tricky to made direct comparisons. We have removed comparison  
12 data from the individual data sets and instead made general comparisons at the very end. I  
13 hope this reads more efficiently and provides better context for our data sets.  
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16 **Comment 3:** Berotralstat is the second-generation oral small molecular inhibitor of plasmatic  
17 kallikrein. Although it was directly designed for HAE LTP, androgens have this indication in their  
18 SPC as well. I would recommend to modify the first phrase in the concluding paragraph.  
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21 **Reply 3:** In the UK, androgens are not licensed for HAE and have just been used off license for  
22 many years. We have also had supply chain issues with danazol and this is not licensed for any  
23 indication now in the UK. I have edited the sentence as androgens may be licensed for this  
24 condition in other countries.  
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### 29 **Response to Reviewer #3**

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31 **Comment 1:** The structure of this letter to the editor is strange as patients mix their results with  
32 data from previous trials which makes the understanding of the real-life-data more difficult. I  
33 would report fist data from the study and then discuss the comparison with previous studies.  
34  
35

36 **Reply 1:** Thank you, we have edited the manuscript to reflect this change.  
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38 **Comment 2:** Also they do not characterize the 54 patients studied – how many female/male/  
39 their age, Type I or II HAE?  
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42 **Reply 2:** We collected limited data in order to keep the survey short and easy to fill in for  
43 patients. Unfortunately, data was not collected for co-morbidities, and we did not receive  
44 enough accurate responses for other demographics to analyse and include in the manuscript.  
45 This will be our focus in future surveys as we wish to find links between any patient factors and  
46 response to berotralstat.  
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51 **Comment 3:** Also, strangely before efficacy they begin by adverse events, reporting also AE  
52 from previous treatments. For me the sentence on adverse effects from danazol seems  
53 inadequate/unnecessary in this manuscript that deals with Berotralstat.  
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3 **Reply 3:** I have moved the results around so we discuss efficacy before treatment failure.

4 During discussions in forums we know that a lot of centres are switching from androgens to  
5 berotralstat and we thought the comparison between adverse effects may be useful. Due to a  
6 restricted word count and other changes made, we have removed the data about danazol from  
7 this manuscript.  
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12 **Comment 4:** The real number of discontinuations is not clear, as apart from the 12/54 there are  
13 other 6 out of which number? This sentence is really mixed: "12 (22%) patients in the survey  
14 stopped treatment before the 6-month analysis compared to 3% reported in the trials<sup>1,3,4</sup>. A  
15 further 6 patients were reported by the submitting centres to have stopped treatment before  
16 the first data point collection. 9 patients stopped treatment due to adverse side effects. 3  
17 patients stopped treatment due to lack of efficacy" – Between the 12 that stopped treatment  
18 they include these additional 6 out of? And then they come back to the causes of  
19 discontinuation in the 12 ....  
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23 **Reply 4:**

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25 We have data from 54 patients, with various patients dropping off through subsequent data  
26 collection points. 12 patients out of these 54 stopped treatment.  
27

28 6 further patients who stopped treatment before the first data collection point are not part of  
29 the 54 and not included in subsequent analyses, and only mentioned for interest. I will clarify  
30 this sentence in the manuscript.  
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35 We hope that the changes and responses above are satisfactory and eagerly await your  
36 feedback.  
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38 Sincerely,

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40 Dr Manisha Ahuja  
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## To the Editor,

**Title:** Berotralstat for the prophylaxis of hereditary angioedema – Real World Evidence data from the United Kingdom

Berotralstat is an oral plasma kallikrein inhibitor, used for routine prevention of attacks of hereditary angioedema (HAE) Type 1 and Type 2. It became available in the UK in November 2020.<sup>1-5</sup> Our objective was to evaluate the real-world clinical outcomes of using this medication. We sent out a patient survey (S1) to obtain information on an estimated 100 UK patients taking Berotralstat 150mg daily. We received 54 responses from 12 UK centres. We collected information on treatment, adverse events, attack frequency, and disease severity, using a questionnaire (S1) beginning 3-months prior to commencing Berotralstat and repeated at 3- and 6-month intervals. This included the validated tool for patient-reported outcome measures, the Angioedema Control Test (AECT).

### *Baseline prophylaxis*

Most patients (32, 59.3%) were receiving prophylaxis prior to starting Berotralstat. 50 % (16) were on attenuated androgens, 37.5% (12) on tranexamic acid (TA) and 6.35% (2) were on both. 6.35% (2) were on C1 inhibitor concentrate. 8 patients (18.6%) had prior prophylactic treatment overlapping with initiation of Berotralstat.

### *Efficacy*

A mixed effect model analysis showed statistically significant reductions in the number of attacks over 6 months during treatment compared with 3 months prior to treatment with berotralstat (6.21±7.07 attacks for months 1-3 of treatment, 4.54±5.49 attacks for months 4-6 vs. 12.91±7.94 attacks for the 3 months prior to treatment;  $P<0.0001$ ,  $n=28-33$ , Figure 1A). This corresponded to a 51.9% and 64.9% reduction for months 1-3 and 4-6, respectively.

### *AECT scores*

AECT scores showed significant improvement in scores from the 3-month prior to treatment compared with 98.6% and 123.8% increases at 1-3- and 4-6-months post treatment, respectively (9.79±4.53 at 1-3 months and 11.03±3.14 at 4-6 months, vs. 4.93±3.42 at baseline;  $P<0.0001$ ,  $n=32-43$ , Figure 1B).

### *Symptom Severity*

Analysis of patient reported severity scores (1 = very mild; 2 = mild, 3 = moderate, 4 = severe and 5 = very severe) showed significant improvement over 6 months of treatment compared with 3 months prior to treatment (2.50±1.21 attacks for months 1-3 of treatment, 2.34±1.17 attacks for months 4-6 vs. 3.47±0.79 attacks for the 3 months prior to treatment;  $P<0.0001$ ,  $n=38-49$ , Figure 1C).

### *Adverse Effects*

In our survey, 22 patients (40.7%) reported abdominal adverse effects (cramps, nausea, diarrhoea and vomiting) and 3 patients reported headaches whilst taking Berotralstat. In patients that continued treatment, symptoms were mild or had resolved by the 6-month survey.

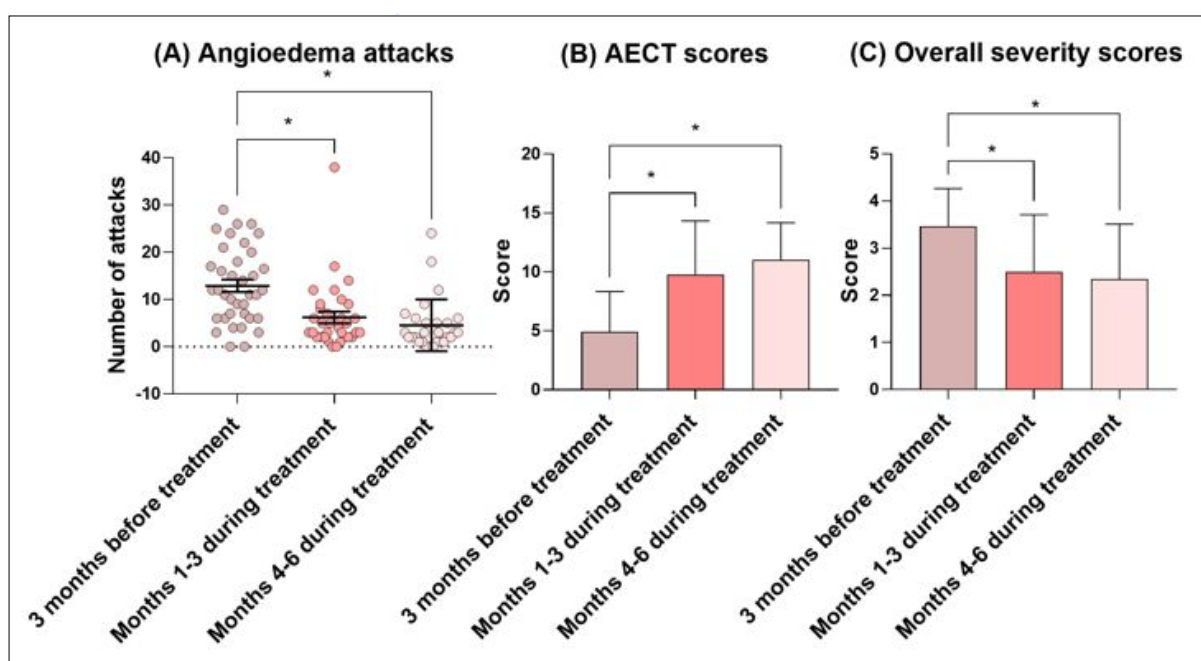
### *Treatment failure*

12 (22%) patients in the survey stopped treatment before the 6-month analysis compared to 3% reported in the trials<sup>1,3,4</sup>. 9 of these patients stopped treatment due to adverse side effects. 3 patients stopped treatment due to lack of efficacy. Although there are no specific monitoring requirements for this medication in the UK<sup>2</sup>, 1 patient who had recently discontinued androgens, discontinued Berotralstat treatment due to deranged liver function tests. A further 6 patients (not

otherwise included in this project) were reported by the submitting centres to have stopped treatment before the first data point collection.

The real-world data provides additional evidence for the efficacy and tolerability of Berotralstat as the first oral prophylactic medication designed specifically for treatment of HAE. Our findings are comparable with previous APeX trials<sup>4</sup> where 58% of the patients had a  $\geq 50\%$  reduction in their HAE attack rates compared to baseline versus 25% of placebo patients. However, our data suggests a higher rate of reported adverse events compared to 21% of patients who reported abdominal pain and 14% reporting diarrhoea in the trials. Further studies are needed to evaluate long term outcomes, and requirement for monitoring blood tests when initiating Berotralstat and discontinuing other prophylactic medications.

## Tables and Figures



**Figure 1.**

A: HAE attack frequency for 3 months prior to initiation of berotralstat treatment and at 1-3 and 4-6 months during treatment. Black lines denote mean $\pm$ SD. \* $P < 0.0001$  vs. baseline;  $n = 28-33$ .

B: Overall AECT scores for 3 months prior to initiation of berotralstat treatment and at 1-3 and 4-6 months during treatment. Black lines denote mean $\pm$ SD. \* $P < 0.0001$  vs. baseline;  $n = 32-43$ .

C: HAE overall severity scores (1-5 with 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe) for 3 months prior to initiation of berotralstat treatment and at 1-3 and 4-6 months during treatment. Black lines denote mean $\pm$ SD. \* $P < 0.0001$  vs. baseline;  $n = 38-49$ .

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1. Manisha Ahuja
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3. Eniola Bode
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1. MA Royal Victoria Infirmary, Newcastle upon Tyne Hospitals
  - . Received honoraria for advisory boards and attending educational events from Takeda and Biocryst.
2. AD: Barts Health NHS Trust
  - . Received an honorarium from Takeda
3. EB Leeds Teaching Hospitals, NHFT
  - . nil
4. APRB Cambridge University Hospitals NHSFT
  - . nil
5. MB Barts Health NHS Trust
  - . nil
6. SC Manchester University NHS Foundation trust
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7. CD Gloucestershire Hospitals NHSFT
    - . nil
  8. SD Leeds Teaching Hospitals, NHSF
    - . nil
  9. AE University Hospitals Birmingham NHSFT
    - . nil
  10. SE Manchester University NHS Foundation Trust
    - . received funds as part of Advisory Board or expert consultation from BioCryst, CSL and Takeda Pharmaceutical Companies
  11. TE Cardiff and Vale UHB
    - . Received educational support, speaker fees and/or advisory board fees from: Allergy Therapeutics, CSL, Novartis, Octapharma, Takeda, Thermo Fisher, Viatrix.
  12. EE University Hospital Southampton NHS Foundation Trust
    - . nil
  13. AH Northern Care Alliance NHS Foundation Trust
    - . Received support for expenses to attend meetings and conferences from BioCryst, CSL Berhing, Pharming, Takeda (previously Shire), Octopharma
  14. TG Manchester University NHS Foundation Trust
    - . Chair of NHS England Clinical Reference Group for immunology and allergy
      - a. Received honoraria from BioCryst, CSL Berhing, Octapharma, Pharming, Takeda (previously Shire) for advisory board and speaking services. Expenses to attend meetings and conferences from BioCryst, CSL Berhing, Pharming, Takeda (previously Shire)
  15. HG University Hospital Southampton NHS Foundation Trust
    - . nil
  16. AG North Bristol Hospitals NHSFT
    - . nil
  17. SG Barts Health NHS Trust
    - . Participation in the APEX-2 clinical trial and expenses to attend conference by Biocryst
  18. RJ Oxford University Hospitals
    - . Funding for attending educational events and for being on advisory board from CSL and Takeda.
  19. LL Barts Health NHS Trust
    - . Received educational grants from Biotest and CSL, advisory and consulting activity with Pharming and speaker's fee from Takeda and Biocryst
  20. AM Cambridge University Hospitals NHSFT
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  21. EM Manchester University NHS Foundation trust
    - . nil
  22. SM St Helier University Hospitals
    - . nil
  23. AM Barts Health NHS Trust
    - . nil
  24. LM University Hospitals Birmingham NHSFT
    - . Honoraria for education event from Biocryst
  25. NP Oxford University Hospitals
    - . nil
  26. KS University Hospitals Birmingham NHSFT
    - . nil
  27. CS Newcastle upon Tyne Hospitals NHSFT

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3 . Received honoraria for education and advisory boards from Biocryst, CSL, Pharming  
4 and Takeda.  
5 28. KT Barts Health NHS Trust  
6 . nil  
7 29. RLY Cambridge University Hospitals NHSFT  
8 . nil  
9 30. PY Frimley Health NHSFT  
10 . Participation in APEX-2 clinical trial and honoraria from Biocryst for education and  
11 advisory boards.  
12 31. SK Barts Health NHS Trust  
13 . Participation in APEX-2 clinical trial and honoraria from Biocryst for education and  
14 advisory boards.  
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### Author Contributions

19 The article above was written by Manisha Ahuja, Sorena Kiani-Alikhan and Patrick Yong.  
20 Data analysis and figures were generated by Anthony Dorr and Manisha Ahuja. All other  
21 authors have collected the raw data for the project as well as edited the final work.  
22  
23  
24

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33 **Funding Statement:** nil declared  
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### Online Supplementary Repository

- 36 • Patient Questionnaire (S1)
  - 37 • AECT scores
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2. [Withdrawn] Berotralstat: Treatment protocol: Information for healthcare professionals [Internet]. GOV.UK. 2022 [cited 10 April 2022]. Available from: <https://www.gov.uk/government/publications/berotralstat-in-the-treatment-of-hereditary-angioedema/berotralstat-treatment-protocol-information-for-healthcare-professionals>
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### *Adverse Effects*

~~In the APeX trials<sup>4</sup> 21% of patients reported abdominal pain and 14% reported diarrhoea. In our survey, 22 patients (40.7%) reported abdominal adverse effects (cramps, nausea, diarrhoea and vomiting) and 3 patients reported headaches whilst taking Berotralstat. In patients that continued treatment, symptoms were mild or had resolved by the 6-month survey. Patients on attenuated androgens prior to initiating Berotralstat had reported weight gain, increased body hair, mood changes and tiredness whilst on androgens alone.~~

### *Treatment failure*

~~12 (22%) patients in the survey stopped treatment before the 6-month analysis compared to 3% reported in the trials<sup>4,3,4</sup>. A further 6 patients were reported by the submitting centres to have stopped treatment before the first data point collection. 9 patients stopped treatment due to adverse side effects. 3 patients stopped treatment due to lack of efficacy. Although there are no specific monitoring requirements for this medication in the UK<sup>2</sup>, 1 patient who had recently discontinued androgens, discontinued Berotralstat treatment due to deranged liver function tests.~~

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A mixed effect model analysis showed statistically significant reductions in the number of attacks over 6 months during treatment compared with 3 months prior to treatment with berotralstat (6.21±7.07 attacks for months 1-3 of treatment, 4.54±5.49 attacks for months 4-6 vs. 12.91±7.94 attacks for the 3 months prior to treatment;  $P<0.0001$ ,  $n=28-33$ , Figure 1A). This corresponded to a 51.9% and 64.9% reduction for months 1-3 and 4-6, respectively. ~~In comparison, the trial data showed that in the 150mg arm, 58% of the patients had a  $\geq 50\%$  reduction in their HAE attack rates compared to baseline versus 25% of placebo patients.~~

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AECT scores showed significant improvement in scores from the 3-month prior to treatment compared with 98.6% and 123.8% increases at 1-3- and 4-6-months post treatment, respectively (9.79±4.53 at 1-3 months and 11.03±3.14 at 4-6 months, vs. 4.93±3.42 at baseline;  $P<0.0001$ ,  $n=32-43$ , Figure 1B).

### Symptom Severity

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### Adverse Effects

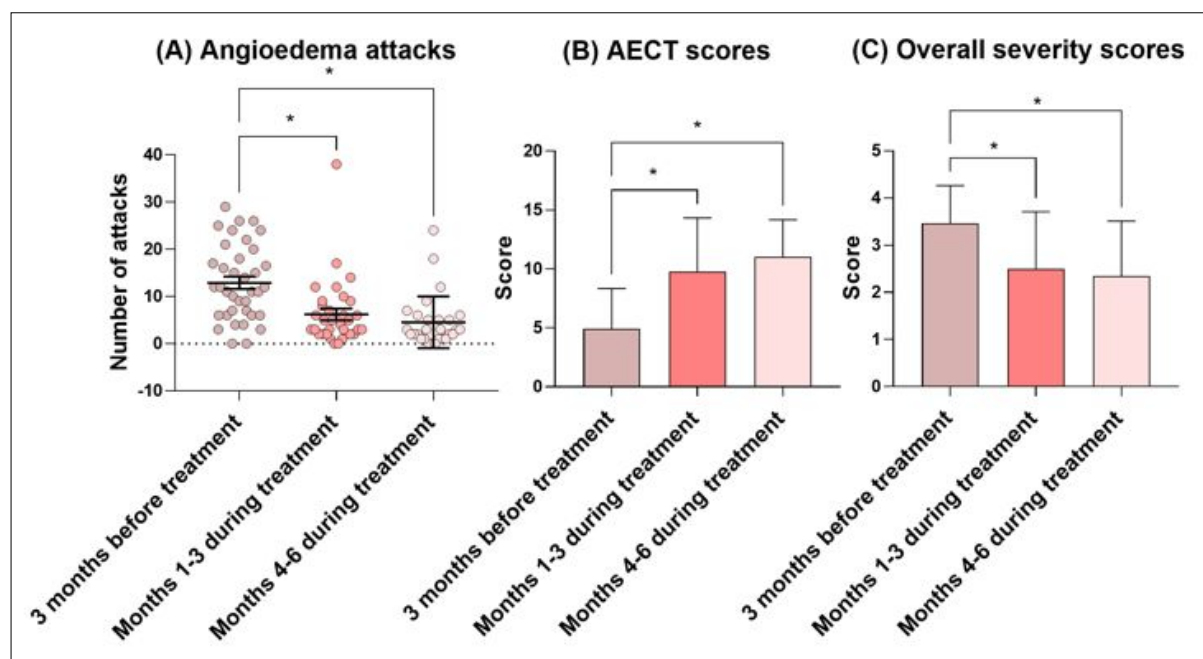
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## Tables and Figures



**Figure 1.**

A: HAE attack frequency for 3 months prior to initiation of berotralstat treatment and at 1-3 and 4-6 months during treatment. Black lines denote mean $\pm$ SD. \* $P$ <0.0001 vs. baseline; n=28-33.

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1. MA Royal Victoria Infirmary, Newcastle upon Tyne Hospitals
  - . Received honoraria for advisory boards and attending educational events from Takeda and Biocryst.
2. AD: Barts Health NHS Trust
  - . Received an honorarium from Takeda
3. EB Leeds Teaching Hospitals, NHFT
  - . nil
4. APRB Cambridge University Hospitals NHSFT
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5. MB Barts Health NHS Trust
  - . nil
6. SC Manchester University NHS Foundation trust
  - . nil

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- 4 7. CD Gloucestershire Hospitals NHSFT
- 5 . nil
- 6 8. SD Leeds Teaching Hospitals, NHSF
- 7 . nil
- 8 9. AE University Hospitals Birmingham NHSFT
- 9 . nil
- 10 10. SE Manchester University NHS Foundation Trust
- 11 . received funds as part of Advisory Board or expert consultation from BioCryst, CSL
- 12 and Takeda Pharmaceutical Companies
- 13 11. TE Cardiff and Vale UHB
- 14 . Received educational support, speaker fees and/or advisory board fees from: Allergy
- 15 Therapeutics, CSL, Novartis, Octapharma, Takeda, Thermo Fisher, Viatrix.
- 16 12. EE University Hospital Southampton NHS Foundation Trust
- 17 . nil
- 18 13. AH Northern Care Alliance NHS Foundation Trust
- 19 . Received support for expenses to attend meetings and conferences
- 20 from BioCryst, CSL Berhing, Pharming, Takeda (previously Shire), Octopharma
- 21 14. TG Manchester University NHS Foundation Trust
- 22 . Chair of NHS England Clinical Reference Group for immunology and allergy
- 23 a. Received honoraria from BioCryst, CSL Berhing, Octapharma, Pharming, Takeda
- 24 (previously Shire) for advisory board and speaking services. Expenses to attend
- 25 meetings and conferences from BioCryst, CSL Berhing, Pharming, Takeda (previously
- 26 Shire)
- 27 15. HG University Hospital Southampton NHS Foundation Trust
- 28 . nil
- 29 16. AG North Bristol Hospitals NHSFT
- 30 . nil
- 31 17. SG Barts Health NHS Trust
- 32 . Participation in the APEX-2 clinical trial and expenses to attend conference by
- 33 Biocryst
- 34 18. RJ Oxford University Hospitals
- 35 . Funding for attending educational events and for being on advisory board from CSL
- 36 and Takeda.
- 37 19. LL Barts Health NHS Trust
- 38 . Received educational grants from Biotest and CSL, advisory and consulting activity
- 39 with Pharming and speaker's fee from Takeda and Biocryst
- 40 20. AM Cambridge University Hospitals NHSFT
- 41 . nil
- 42 21. EM Manchester University NHS Foundation trust
- 43 . nil
- 44 22. SM St Helier University Hospitals
- 45 . nil
- 46 23. AM Barts Health NHS Trust
- 47 . nil
- 48 24. LM University Hospitals Birmingham NHSFT
- 49 . Honoraria for education event from Biocryst
- 50 25. NP Oxford University Hospitals
- 51 . nil
- 52 26. KS University Hospitals Birmingham NHSFT
- 53 . nil
- 54 27. CS Newcastle upon Tyne Hospitals NHSFT
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3 . Received honoraria for education and advisory boards from Biocryst, CSL, Pharming  
4 and Takeda.  
5 28. KT Barts Health NHS Trust  
6 . nil  
7 29. RLY Cambridge University Hospitals NHSFT  
8 . nil  
9 30. PY Frimley Health NHSFT  
10 . Participation in APEX-2 clinical trial and honoraria from Biocryst for education and  
11 advisory boards.  
12 31. SK Barts Health NHS Trust  
13 . Participation in APEX-2 clinical trial and honoraria from Biocryst for education and  
14 advisory boards.  
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### 19 **Author Contributions**

20 The article above was written by Manisha Ahuja, Sorena Kiani-Alikhan and Patrick Yong.  
21 Data analysis and figures were generated by Anthony Dorr and Manisha Ahuja. All other  
22 authors have collected the raw data for the project as well as edited the final work.  
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### 36 **Online Supplementary Repository**

- 37 • Patient Questionnaire (S1)
- 38 • AECT scores
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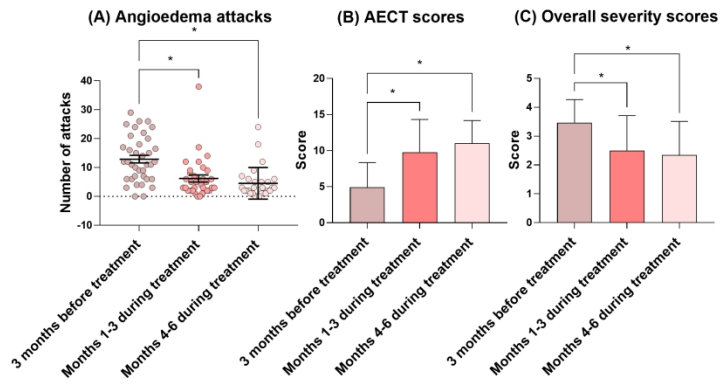
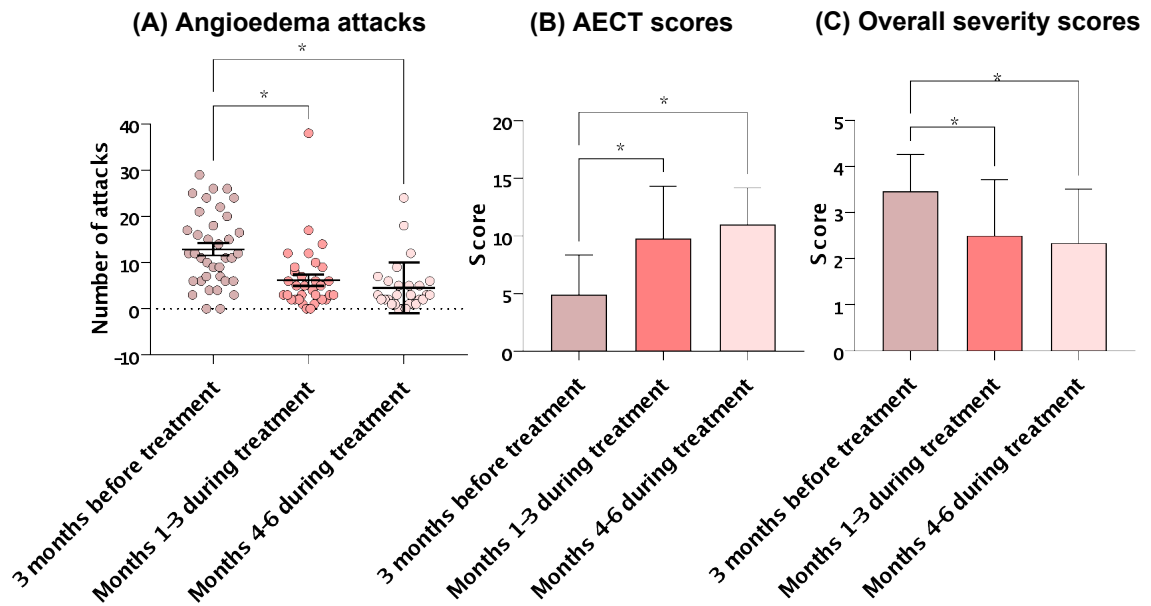


Figure 1\_ Ahuja et al.

483x698mm (130 x 130 DPI)



**Figure 1.**

A: HAE attack frequency for 3 months prior to initiation of berotralstat treatment and at 1-3 and 4-6 months during treatment. Black lines denote mean $\pm$ SD. \* $P$ <0.0001 vs. baseline; n=28-33.

B: Overall AECT scores for 3 months prior to initiation of berotralstat treatment and at 1-3 and 4-6 months during treatment. Black lines denote mean $\pm$ SD. \* $P$ <0.0001 vs. baseline; n=32-43.

C: HAE overall severity scores (1-5 with 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe) for 3 months prior to initiation of berotralstat treatment and at 1-3 and 4-6 months during treatment. Black lines denote mean $\pm$ SD. \* $P$ <0.0001 vs. baseline; n=38-49.

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## AECT Scores

**Angioedema Control Test**

**How often have you had an HAE attack? (0 – 4)**

very often/ often/ sometimes/ seldom/ not at all

**How much has your quality of life been affected by your HAE? (0 - 4)**

very much / much / somewhat/ a little / not at all

**How much has the unpredictability of your HAE bothered you? (0 - 4)**

very much / much / somewhat / a little / not at all

**How well is your HAE controlled by your current treatment? (0 - 4)**

Not at all / a little / somewhat / much / very well

**Figure 1:** Questions in the Angioedema Control Test (AECT). A maximum score of 16 is possible. A score of 10 or more suggests well-controlled symptoms of recurrent angioedema.

**Figure 1:** Questions in the Angioedema Control Test (AECT). A maximum score of 16 is possible. A score of 10 or more suggests well-controlled symptoms of recurrent angioedema.





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- c. How much has the unpredictability of your HAE bothered you? (1 – 5)  
**3 months prior:** very much / much / somewhat / a little / not at all  
**1 month after starting?:** very much / much / somewhat/ a little / not at all  
**3 months after starting?:** very much / much / somewhat/ a little / not at all  
**6 months after starting?:** very much / much / somewhat/ a little / not at all
- d. How well is your HAE controlled by your current treatment? ( 1 – 5)  
**3 months prior:** Not at all / a little / somewhat / much / very well  
**1 month after starting?:** Not at all / a little / somewhat / much / very well  
**3 months after starting?:** Not at all / a little / somewhat / much / very well  
**6 months after starting?:** Not at all / a little / somewhat / much / very well
3. **How would you describe the overall severity of HAE attacks in the three months**
- a) **prior to starting Berotralstat? (please circle)**  
 0. No attacks/not applicable 1. Very Mild 2. Mild 3. Moderate 4. Severe 5. Very severe
- b) **1 months after starting Berotralstat? (please circle)**  
 0. No attacks/not applicable 1. Very Mild 2. Mild 3. Moderate 4. Severe 5. Very severe
- c) **3 months after starting Berotralstat? (please circle)**  
 0. No attacks/not applicable 1. Very Mild 2. Mild 3. Moderate 4. Severe 5. Very severe
- d) **6 months after starting Berotralstat? (please circle)**  
 0. No attacks/not applicable 1. Very Mild 2. Mild 3. Moderate 4. Severe 5. Very severe
4. **How many times did you use rescue medications during the last 3 months before Berotralstat?**
- a) Icatibant  
 b) C1- esterase inhibitor
5. **What medication were you taking in the last three months as prophylaxis just before Berotralstat (multiple choices can be picked)**
- a. None  
 b. Tranexamic acid  
 c. Danazol  
 d. Oxandrolone  
 e. Regular C1-Inhibitor (for prophylaxis only)  
     i. Frequency of administration .....

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6. **If you were not on prophylaxis before starting Berotralstat, have you ever been on any prophylaxis?**

**No: go to Q 15**

Yes:

- a. Which one .....
- b. What dose .....
- c. When .....
- d. For how long .....

7. **Where there any other reasons to stop androgen treatment?**

- a. side effects
- b. fear of side effects
- c. lack of efficacy
- d. Abnormal blood tests or scans
- e. (planned) pregnancy
- f. other reasons .....
- g. No other reasons
- h. Not applicable

8. **If you were taking Danazol or Oxandrolone, did you experience any side effects?**

- a. Weight gain
- b. Acne
- c. Altered libido
- d. Virilization
  - i. Voice changes
  - ii. Increased body hair
  - iii. Reduced breast size
  - iv. Change in genitals
  - v. More muscles (athletic type)
  - vi. Laryngeal prominence (enlargement of Adam's apple)
- e. Muscle cramps
- f. Menstrual irregularities
- g. High blood pressure
- h. Headache
- i. Increased sweating or outbreaks of sweating
- j. Psychological abnormalities
  - i. Depression
  - ii. Aggressiveness
  - iii. Tiredness
  - iv. Panic attacks
  - v. Mood changes
- k. Fast heart rate or palpitations
- l. Joint pain
- m. Generalized itching
- n. Early puberty
- o. No side effects at all
- p. Other ...
- q. Not applicable

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3 **9. If you did stop androgens, how did you do it?**  
4

- 5 a. The androgens were gradually decreased in dosage until the treatment was stopped  
6 b. The androgens were stopped in one day  
7 c. Not applicable  
8  
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10 **10. Was there an overlap between your previous treatment and Berotralstat**  
11

- 12 a. Yes  
13 i. How long?.....  
14 b. No  
15

16 **11. Was there a gap between your previous treatment and Berotralstat**  
17

- 18 a. Yes  
19 i. How long?.....  
20 b. No  
21  
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23 **12. Which changes did you notice after stopping androgen treatment? How long did it take to improve?**  
24  
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Symptom	Duration take to improve? Choose from days, weeks, months or ongoing
Fatigue	
Myalgia (muscle pain)	
Arthralgia (joint pain)	
Headache	
Insomnia	
Emotional lability	
Anxiety	
Depression / depressive phase	
Apathy	
Eating disorder	
Temporary increase in hereditary angioedema attacks	
None	
Other	

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47 **13. If you were on androgens, how many HAE attacks did you have after stopping Androgens and before starting Berotralstat**  
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- 49 a. In the first month  
50 b. In the second month  
51 c. In the 3<sup>rd</sup> month  
52 d. From 3 to 6 months after stopping  
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56 **14. If you were on any other prophylaxis prior to starting Berotralstat, why was this stopped?**  
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58 .....  
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15. How many HAE attacks have you had after starting Berotralstat

- a. In the first month :
- b. In the second month
- c. In the 3<sup>rd</sup> month:
- d. From 3 to 6 months after starting

16. Have you had any new symptoms that you think may be due to starting Berotralstat

- a. No
- b. Yes
  - i. Please describe the symptom(s)
  - ii. How long after starting Berotralstat did you experience this
  - iii. How long did it last
  - iv. If it is recurring, how often do you have this/these new symptom(s)
  - v. If you stopped taking Berotralstat due to new symptom(s), how long after starting this medication, did you do this?



Questions 17 to be answered by Immunology staff

17. Have you reported all adverse events (rather than reactions, which might imply we only want the ones considered related) to Biocryst, with the EAMS Biocryst reporting link?

- a. Yes
- b. No

If the answer is yes, please provide date of report:.....

For Peer Review

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