Clinical Study Report Synopsis

Study Code	D3250R00061
Version	1.0
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TWINKLE: Real-Life First Dose Effect of Fasenra in Patients With Severe Uncontrolled Asthma

Milestones:

Study design concept	17 April 2019
Final Protocol, version 1.0	30 May 2019
Final Protocol, version 2.0	25 July 2019
First patient first visit	20 December 2019
Last patient last visit	09 April 2020
Statistical analysis plan	24 March 2020
Database lock	06 July 2020

Phase of Development: Observational, real world evidence study

Sponsor: AstraZeneca

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This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Background/rationale:

In clinical practice, the first dose effect of biologics is typically evaluated using Patient Reported Outcome (PRO) measures eg, Asthma Control Questionnaire (ACQ) or St. 'George's Respiratory Questionnaire (SGRQ), and spirometry at the 4-week office visit following initial injection. Anecdotally, patients report feeling physically and mentally better, and an improvement in their quality of life (QoL) much earlier than 4 weeks but this is individualised to each patient and is rarely captured in a clinical setting.

Tools such as mobile applications can offer additional channels for collecting information from patients about their QoL, symptoms and well-being in a patient-centric manner. Digitally capturing the patient experience on a daily basis may allow us to develop new endpoints that could be used in clinical studies, to create a clinical tool for healthcare practitioners and their patients to track treatment response.

This pilot study used novel technologies to collect information about the 'patient's experience before and early after starting Fasenra as standard of care for severe uncontrolled asthma in a real world setting to determine how the experience changes over time. Any detection of an early, subjective first dose effect in this pilot study will be further validated in a larger follow-up study.

Current PROs do not currently capture subtle changes in a 'person's mood and well-being on a daily basis in order to show when the patients first regain their "twinkle", a marked improvement in their symptoms and/or QoL. Using video capture and facial analysis technology in conjunction with a daily questionnaire and spirometry, the aim of the study was to capture these subtle changes over time while supplementing the information obtained from validated PROs.

Objectives:

Primary objectives and hypotheses: To explore the use of novel technologies to detect early changes in QoL within the first 4 weeks after first dose of Fasenra for the treatment of severe uncontrolled asthma.

Secondary objectives and hypotheses:

- To explore changes in QoL and asthma symptom biomarkers over time using novel measurements as compared to outcomes captured via validated PROs and lung function
- To evaluate which biomarkers show earliest impact on QoL and positive patient experience
- To explore potential composites of outcome variables to detect early improvement in QoL
- To explore time of onset for subjectively measured changes in QoL as compared to changes in lung function

- To evaluate patient experience and compliance with technology and applications (apps) during daily monitoring
- To explore the relationship between message topics, impact on daily life and coping strategies as captured via the PROACT system

Study design: This was an observational, real world evidence study. No treatments were provided by the Sponsor. Fasenra was prescribed by the treating physician per standard of care. All data collected was for the purpose of evaluating an individual 'patient's daily QoL and well-being. Normal communication channels and responsibilities of care between patients and their ongoing medical practitioner were maintained unaltered throughout their participation in this observational study.

This was planned as a small pilot study on 10 adult patients with severe uncontrolled asthma who would begin Fasenra as standard of care. Patients were enrolled at a single site in London, UK and asked to provide their feedback on their asthma treatment using the questionnaires and devices provided for this purpose. Enrolled patients were onboarded and the daily tasks they were to perform at home during the study were explained. Patients were asked to record data for 2 weeks prior to their first Fasenra injection (Run-in period) and then for 4 more weeks post-injection. The estimated study duration per patient was approximately 6 weeks from the enrolment visit to end of recorded data. Patients were required to visit the study site 3 times during the study: for enrolment and onboarding visit, Fasenra injection, and the end of study visit.

The end of study was defined as the last expected visit/contact of the last patient undergoing the study. A patient was considered to have completed the study when the patient completed the last scheduled visit.

Data source: Patient data was collected via medical records, pre- and post-study surveys; questionnaires ACQ-6 and SGRQ; clinical app PROACT; the health data capture platform questionnaire uMotif; and iSpirometry using MIR Spirobank Smart® spirometer.

Study population: For this small pilot study, 10 patients were planned to be recruited from one site in London, England. Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, were not permitted.

Inclusion criteria: The important inclusion criteria are listed below. Included patients met all of the inclusion criteria and none of the exclusion criteria.

- Individuals aged 18-75 years with severe asthma uncontrolled (ACQ $\geq$ 1.5) on current medications (HD-ICS/LABA with/without other maintenance therapies except biologics).
- Individuals beginning Fasenra as standard of care as specified by NICE guidelines, ie, patients having either 4 exacerbations in the previous year and an eosinophil count > 300 cells/microliter OR 3 exacerbations in the previous year and an eosinophil count > 400 cells/microliter.
- Individuals who have a smartphone that is compatible with the device software (iOS and Android)

Exclusion criteria: Patients were excluded if any of the following criteria were fulfilled:

- Individuals taking daily prednisolone or equivalent

- Individuals currently taking a biologic medication or participating in a clinical study involving a biologic medication for a respiratory illness
- Individuals with comorbid conditions that cause symptoms similar to those experienced with asthma (eg, cough, wheeze, breathlessness, or night-time awakening)
- Individuals with comorbidities that also significantly affect QoL and daily functioning as determined by the treating physician
- Individuals with other chronic pulmonary conditions (eg, COPD)
- Individuals that in the opinion of the physician are unlikely to complete 6 weeks of the study (example reasons: digital literacy, unwillingness/inability to interact with apps; historically poor adherence to study procedures)

Statistical methods:

This was an exploratory pilot study to assess the potential for using novel technology and novel measurements in assessing early onset of effect following initiation of Fasenra as the new standard of care treatment in severe asthma patients. Given that both the technology and measurements are not well studied, and that no standardised outcome variables have been established the study is descriptive in nature, without evaluation of any pre-defined tests.

All enrolled patients who received at least one dose of Fasenra comprised in the Full Analysis Set (FAS). Patients were analysed irrespective of whether or not they prematurely discontinued, according to the intent-to-treat (ITT) principle. All analyses were performed on the FAS.

Baseline measurements were captured during the run-in period. If there was no data prior to the first dose of Fasenra, then the patient was withdrawn from the study.

Data on demographics, baseline measurements, medical history, pre-study survey, treatment history and post-study survey are listed. All outcomes are listed and presented using graphical displays.

The PRO outcome data are assessed descriptively through listings and graphical presentations. Further exploratory work to assess relationships between the different PRO methods was assessed using various graphical displays and statistical modelling.

Data summaries were originally planned. However due to the small number of patients recruited, data is mainly displayed through listings and graphical presentations.

The Primary objective to explore the use of novel technologies to detect early changes in QoL within the first 4 weeks after first dose of Fasenra for the treatment of severe uncontrolled asthma was assessed using data obtained from daily PROACT, uMotif and spirometry tools. The PROACT system was used to assess QoL using facial recognition and sentiment analysis to determine changes in 'patients' emotions as a subjective measure of effects of the first dose of Fasenra. The onset of changes and size of effect for the different techniques and tools was

assessed based on listings and graphical presentations of the individual patients daily scores compared to baseline.

The analysis for secondary objectives included:

- The use of novel techniques was compared with more traditional methods (ACQ-6 and SGRQ). The onset of changes and size of effect based on ACQ-6 and SGRQ was assessed based on listings and graphical presentations of the individual patients scores compared to baseline. Patients were also assigned a "response" status for ACQ-6 and SGRQ.
- Compliance of the different techniques was also assessed based on the number of days with non-missing assessments for each outcome.
- To explore which techniques show the earliest impact on QoL and positive patient experience and also potential composites of outcome variables to detect early improvements in QoL, associations between any onset of effect seen for PROACT, uMotif and spirometry measures and validated PROs (ACQ-6 and SGRQ) were explored descriptively using different graphical displays and statistical models. Correlations between the different techniques were also explored. Criteria were respectively defined to categorise responders taking account of data across all the different techniques. A responder was defined as a patient with a change from baseline in ACQ-6 score of ≤ -0.5 or a change from baseline in SGRQ total score of < -4.0 at the end of study.

Results:

Study participation:

Due to the COVID-19 pandemic, this study was terminated early. At the time of study termination, 4 of the 5 enrolled patients were evaluable, which was approximately 40% of the targeted sample size. Due to this, all analyses planned were not performed. However, an exploratory analysis was performed for data collected from the 4 evaluable patients, which summarised descriptions of visualisations of digital measurements for each individual patient. These exploratory analyses helped understand which measurements using novel technology were the best indicators of early improvement in QoL within 4 weeks after the first Fasenra injection.

The 5 enrolled patients aged between 24 and 67 years, and 1 patient was male and 4 were females

Main Results:

Exploratory analyses of these data were done to understand if significant improvements in QoL could be observed as early as within 1 week after Fasenra injection. Scores from the novel digital PROs (spirometry, uMotif and PROACT) were analysed and correlated with scores from the validated PROs (ACQ-6 and SGRQ). These analyses were based on a small sample size (4 patients) and must not be generalised. It must also be noted that minor deviations from the study protocol including relaxed inclusion criteria, delayed Fasenra injection, delayed site-visit, and delayed SGRQ reporting were tolerated in these analyses.

Three (3) of the 4 evaluable patients showed a response within the first 1 to 2 weeks after receiving the Fasenra injection, indicated by a positive change in the 3 novel digital PRO scores (spirometry, uMotif and PROACT sentiment) and were designated as "responders". A "twinkle" day was defined as a day at which a confirmed positive response was observed on the 3 novel digital PRO scores. By this definition, a confirmed positive response was observed within 2 to 4 days after receiving the Fasenra injection in all 3 responder patients. In general, the "twinkle" could be observed as early as within 48 hours after receiving Fasenra, while a full response could be seen after about 10-14 days. It should be noted that "twinkle"/early response was retrospectively defined, and might have generated twinkle events due to day-to-day variations in the PRO scores, particularly given the correlation seen between endpoints.

The correlation between the weekly ACQ-6 and the weekly-aggregated uMotif and spirometry scores was strong, indicating that at home-based PRO measures, such as uMotif and iSpirometry, could be used to support early identification of treatment response. Home-based daily questionnaires via uMotif correlated strongly with traditional ACQ-6/SGRQ sores and captured significant improvements within the first week for all 3 responder patients. Home-based spirometry, especially the measurement of PEF, was reliable for identifying significant improvements in lung function.

As part of this pilot study, basic implementations of Microsoft Azure services were used to analyse PROACT data by deriving sentiment scores from transcribed text and emotion scores from self-recorded videos. It was noted that the algorithm used for sentiment analysis is not validated for analysing medical information. Upon studying the PROACT scores, some discrepancies were observed between the PROACT sentiment scores and the actual messages the patients expressed. This was likely because of limitations in the proprietary algorithms for text and emotion detection used for PROACT analysis. Since the PROACT code is not publicly available, its application to the clinical/healthcare domain cannot be clearly assessed at this point. However, numerous open-source databases for speech, audio and video could be used to develop custom and patient specific algorithms to personalise sentiment and emotion input. This provides a background and opportunity for an in-depth literature review and evaluation of personalised natural language processing methods suitable for medical information (e.g. Amazon Comprehend Medical) in both controlled research and development settings as well as in follow-on studies. Also, the PROACT emotion data were noisy, as expected, with each patient seeming to have a personalised baseline of emotions. The regression models used to mitigate the influence of personal emotional baselines indicated that emotion scores are meaningful and reflect the sentiment of the message being delivered. This revealed a scope to further develop these models for application in future clinical studies, and explore predicting other variables than the sentiment/emotion, e.g. general QoL.

While none of the patients had participated in a clinical study using "wearable" devices, all patients found it easy to use the devices and home-based PRO applications and reported positive experiences using these applications. All patients reported that the devices and novel applications were convenient to use and were not burdensome to their daily life.

Although the small sample size reduced the generalizability of the findings, the results are promising for both sentiment and emotion-based artificial intelligence applications, and exploratory results from this study can be informative for design considerations in designing subsequent studies with many more patients. This brings to attention an opportunity in the sentiment and emotion-AI space that should be further explored in both controlled R&D settings as well as in follow-on studies

Safety evaluation:

No medicinal products were evaluated directly for safety purposes in this study

Conclusion:

Three (3) of the 4 evaluable patients in this study showed signs of improvement in their asthma symptoms and QoL as early as within the first week after the Fasenra injection, as assessed using the novel digital PROs. Although the digital PROACT sentiment and emotion analyses faced technological limits and personal biases, significant QoL improvements could still be identified. Furthermore, the correlation between the validated weekly ACQ-6 scores and the novel weekly-aggregated uMotif scores, PROACT sentiment scores, and spirometry scores was strong, indicating that home-based PRO measures could be used to support early identification of treatment response.

Publications: None