Extrapulmonary Disease Burden and Impact of Cystic Fibrosis on Productivity in People With Cystic Fibrosis Aged ≥12 Years Not Treated With Cystic Fibrosis Transmembrane Conductance Regulator Modulators: Interim Analysis of the HUBBLE Study

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BACKGROUND

- Managing cystic fibrosis (CF) is a daily commitment for people with CF (pwCF); the symptoms and complications of CF contribute to high illness burden and negatively impact quality of life[1-4]
- Currently, there are limited data available on the extrapulmonary burden of CF from the perspective of pwCF
- HUBBLE is a real-world, observational study assessing the impact of CF and CF transmembrane conductance regulator modulator (CFTRm) therapy on patient-reported outcomes (PROs)
- Here, we present a preplanned, cross-sectional, interim analysis of extrapulmonary symptom burden and work/school productivity impact of CF at enrolment from the HUBBLE study in pwCF not receiving CFTRm therapy

OBJECTIVE

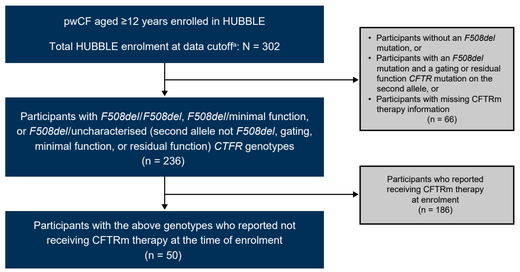
- **To evaluate the extrapulmonary symptom burden and impact of CF on work/school productivity in pwCF aged ≥12 years with specific *CFTR* genotypes not receiving CFTRm therapy**

METHODS

Study Design

- HUBBLE is a prospective, longitudinal, real-world study of 18 months' duration in pwCF aged ≥6 years
- Participants were recruited using social media advertising and direct outreach by patient volunteers who belong to a CF-specific online community (cftechnology.org)
- All data, including demographics, genotype, percent predicted forced expiratory volume in 1 second ($ppFEV_1$), CF treatments, and PROs, were self-reported
- This preplanned, interim analysis of extrapulmonary symptom burden and work/school productivity impact is a descriptive cross-sectional summary of data collected at the time of enrolment and included a subset of pwCF enrolled in HUBBLE in Germany, Ireland, and the UK who met specific criteria (**Figure 1**)
  - This interim analysis assessed PROs using disease-specific measures and questions on sinus or nasal symptoms (**Table 1**) that were completed by participants at enrolment through a web-based platform accessed via internet-enabled devices
  - Data for this interim analysis were collected between October 2020 and April 2021
- This study was reviewed and approved by Salus IRB and the Irish College of General Physicians Ethics Committee

Figure 1. Cohort Selection



CFTRm: cystic fibrosis transmembrane conductance regulator modulator; pwCF: people with cystic fibrosis.
[a] Data cutoff date: 9 April 2021.

Statistical Analysis

- All data were summarised using descriptive statistics. No formal statistical hypothesis testing was performed

Table 1. Outcomes

Assessment	Description	Recall period
Sinus or nasal symptoms questions	• Questions that assess sinus or nasal symptoms, their frequency, and degree of bothersomeness • Symptoms recorded are blocked or stuffy nose or ear, runny nose, pain around the eyes or forehead, mucous in the throat or needing to clear the throat, thick or green/yellow nasal discharge, and other	Past 14 days
CF Abdominal-Score (CFAbd-Score) questionnaire[5]	• CF-specific, 28-item, validated questionnaire that assesses gastrointestinal symptoms[5] • Domains include pain, bowel movement disorders, eating and appetite disorders, reflux symptoms, and impairment of health-related quality of life • Scores range from 0 to 100, with higher scores indicating worse symptoms	Past 14 days
Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions – Specific Health Problem (WPAI-CIQ-SHP)[6]	• Ten-item questionnaire that assesses work or school presenteeism and absenteeism, overall work or school productivity, and impairment in daily activities due to CF • Work/school productivity loss was defined as the percentage of usual productivity lost at work/school due to both absenteeism (mean percentage of time missed from work/school due to CF) and presenteeism (mean percentage of impairment while working/attending school) due to CF • Scores range from 0% to 100%, with higher scores indicating worse impairment	Past 7 days

CF: cystic fibrosis.

Table 2. Demographics and Clinical Characteristics at Enrolment

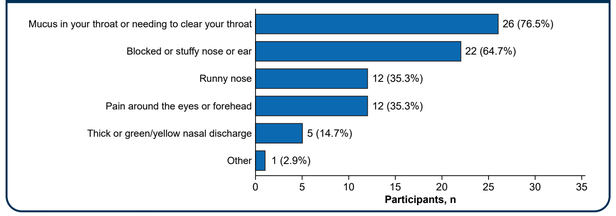
	HUBBLE IA population N = 50
Sex, n (%)	
Male	16 (32.0)
Female	34 (68.0)
Age at registration, mean (SD), years	29.2 (9.8)
12-17 years, n (%)	8 (16.0)
≥18 years, n (%)	42 (84.0)
Participant location, n (%)	
Ireland	12 (24.0)
Germany	25 (50.0)
UK	13 (26.0)
***CFTR* genotypes, n (%)**	
F508del/*F508del*	25 (50.0)
F508del/minimal function	11 (22.0)
F508del/uncharacterised[a]	14 (28.0)
$ppFEV_1$, mean (SD)	74.9 (25.4)
$ppFEV_1$ categories, n (%)	
<40	4 (8.9)
≥40 to <70	14 (31.1)
≥70 to ≤90	15 (33.3)
>90	12 (26.7)
Missing	5
CFQ-R respiratory domain score, mean (SD), points	68.0 (19.3)

CFQ-R: Cystic Fibrosis Questionnaire-Revised; IA: interim analysis; ppFEV$_1$: percent predicted forced expiratory volume in 1 second.
[a] *F508del*/uncharacterised refers to *F508del* heterozygous genotypes with the second allele containing any mutation except for *F508del*, gating mutations, minimal function mutations, or residual function mutations.

RESULTS

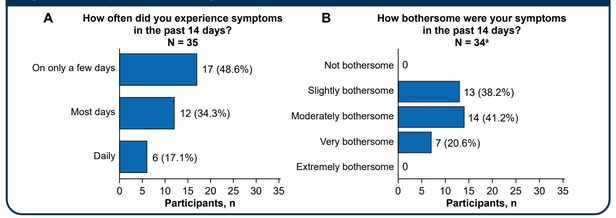
- Demographics and clinical characteristics of the participants are shown in **Table 2**
- Sinus or nasal symptoms in the past 14 days were reported by 35 of 50 (70%) participants (**Figure 2 and Figure 3**)
  - Approximately half of the participants experienced these symptoms most days or daily, and more than half felt that these symptoms were moderately or very bothersome
- The mean (SD) CF Abdominal-Score (CFAbd-Score) was 30.7 (16.2) for symptoms experienced in the past 14 days (**Table 3 and Figure 4**); as a reference, healthy people without CF are reported to have a mean (SE) total CFAbd-Score of 8.0 (0.7)[5]
  - Flatulence, foul-smelling stools, abdominal pain, need for forced feeding, lack of appetite, abdominal bloating, or fatty stools were experienced by >20% of participants as often as 4-7 times in the past 14 days to daily for the past 14 days
- Mean productivity loss due to CF in the past 7 days was 46.1% for 15 participants who were employed and 33.0% for 11 participants attending school (**Figure 5**)
  - Additionally, mean impairment in daily non–work/school activities due to CF was 33.3% for 45 participants

Figure 2. Reported Symptoms Among Participants Experiencing Sinus or Nasal Symptoms in the Past 14 Days (N = 34[a])



[a] In the 35 participants who answered "Yes" to experiencing sinus or nasal symptoms, 1 had missing information for this question.

Figure 3. Frequency and Degree of Bothersomeness of Sinus and Nasal Symptoms



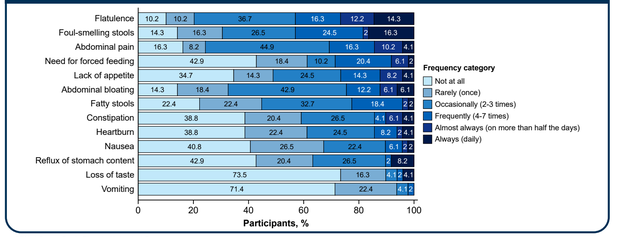
[a] In the 35 participants who answered "Yes" to experiencing sinus or nasal symptoms, 1 had missing information for this question.

Table 3. CFAbd-Score in the Past 14 Days

CFAbd-Scores	Mean (SD) N = 49[a]
Total score	30.7 (16.2)[b]
Domain scores	
Impairment of QoL	30.9 (21.5)
Pain symptoms	35.0 (20.6)
Disorders of bowel movement	33.6 (16.0)
Disorders of eating and appetite	19.6 (16.7)
Gastro-oesophageal reflux symptoms	29.4 (22.3)

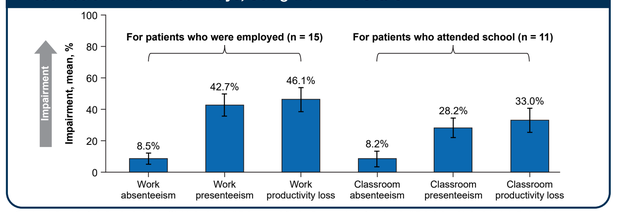
CFAbd-Score: Cystic Fibrosis Abdominal-Score; IA: interim analysis; QoL: quality of life.
[a] One participant had missing information for this question.
[b] As a reference, healthy people without CF have a mean (SE) total CFAbd-Score of 8.0 (0.7).[5]

Figure 4. Individual Abdominal Symptoms[a] by Frequency in the Past 14 Days (N = 49)



CFAbd-Score: Cystic Fibrosis Abdominal-Score.
[a] Assessed using the CFAbd-Score.[5]

Figure 5. Work/School Productivity Loss, Including Work/School Absenteeism and Presenteeism in the Past 7 Days, Using the WPAI-CIQ-SHP



Error bars in the plot refer to the standard errors. Work/school productivity loss was defined as the percentage of usual productivity lost at work/school due to both absenteeism (mean percentage of time missed from work/school due to CF) and presenteeism (mean percentage of impairment while working/attending school) due to CF.
WPAI-CIQ-SHP: Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions–Specific Health Problem.

STUDY LIMITATIONS

- Data on clinical characteristics, such as genotype and $ppFEV_1$, and treatments were all self-reported and not verified
- Data for the study were collected during and could be impacted by the SARS-CoV-2 pandemic
- Study findings may be impacted by potential sample selection bias owing to: (a) selection of a sub-group of pwCF not on CFTRm therapy at the time of enrolment from a larger pool of enrolled pwCF, (b) the need for an internet-enabled device to participate in the study, and (c) recruitment via social media advertising
- The small sample size, especially of pwCF working/attending school, may affect the generalisability of study findings

CONCLUSION

- **Overall, evidence from this real-world study suggests that pwCF aged ≥12 years with *F508del*/*F508del*, *F508del*/minimal function, or *F508del*/uncharacterised *CFTR* genotypes who are not treated with CFTRm therapy experienced substantial extrapulmonary disease burden and a negative impact on work/school productivity and daily activities**

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