A PHASE 3B, OPEN-LABEL, EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY OF ONCE-DAILY DUAL-RELEASE HYDROCORTISONE IN PATIENTS WITH ADRENAL INSUFFICIENCY

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INTRODUCTION

- Patients with adrenal insufficiency (AI) require lifelong glucocorticoid replacement therapy. Standard treatments are unable to replicate the daily physiological cortisol profile, potentially leading to adverse metabolic, cardiovascular and sleep consequences.[1–4]
- In addition, quality of life (QoL) continues to decline over time with conventional treatment in patients with AI.[5]
- The recently introduced once-daily (OD), dual-release hydrocortisone (DR-HC) tablet has demonstrated a more physiological cortisol time–exposure profile than conventional treatment.[6,7]
- DR-HC therapy has been shown to significantly improve cardio-metabolic factors and QoL compared with conventional treatment.[5,7–8]

AIMS

- To investigate the long-term safety and tolerability of DR-HC OD in patients with primary AI.

METHODS

- This was an open-label, multicentre, long-term extension study in adult patients with primary AI receiving stable glucocorticoid replacement therapy (Figure 1).
- Patients received oral DR-HC each morning in the fasted state, using the same total daily dose of hydrocortisone as they were receiving at enrolment.
  - Dose could be adjusted according to the treating physician's judgement.

Outcomes

- Safety and tolerability outcomes included adverse events (AEs), intercurrent illness episodes, increased hydrocortisone need, laboratory parameters, vital signs, and results of patient/investigator questionnaires.
- QoL was evaluated using the Fatigue Impact Scale (FIS) and the Psychological General Well-Being (PGWB) questionnaire.

Statistical analyses

- All statistical analyses were performed on the safety population, i.e. all patients who received ≥ 1 dose of DR-HC.
- Subgroup analyses included patients recruited from the randomized crossover plus 6-month extension study, newly recruited patients and patients with diabetes mellitus (DM). DM was defined as DM during the 5-year extension study.
- Exploratory analyses evaluated change over time using the Wilcoxon signed rank test.

RESULTS

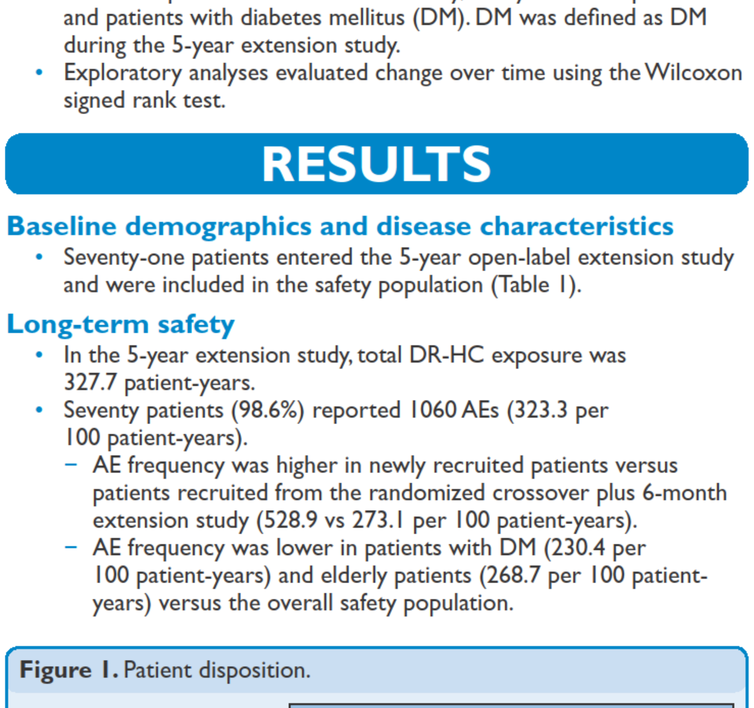
Baseline demographics and disease characteristics

- Seventy-one patients entered the 5-year open-label extension study and were included in the safety population (Table 1).

Long-term safety

- In the 5-year extension study, total DR-HC exposure was 327.7 patient-years.
- Seventy patients (98.6%) reported 1060 AEs (323.3 per 100 patient-years).
  - AE frequency was higher in newly recruited patients versus patients recruited from the randomized crossover plus 6-month extension study (528.9 vs 273.1 per 100 patient-years).
  - AE frequency was lower in patients with DM (230.4 per 100 patient-years) and elderly patients (268.7 per 100 patient-years) versus the overall safety population.

Figure 1. Patient disposition.



AE, adverse event; DR-HC, dual-release hydrocortisone; HC, hydrocortisone; OD, once daily; SAE, serious adverse event; TID, three times daily.
[a]At each assessment, patients had a full clinical examination, study drugs were dispensed and patient questionnaires were collected; [b]newly recruited patients had additional assessments at 4 weeks (by telephone) and 3 months (at the clinic).

Table 1. Demographic and baseline characteristics: safety population.

	All patients (n = 71)	Subgroups by recruitment status		Patients with DM[b] (n = 14)
		From previous study[a] (n = 55)	Newly recruited (n = 16)	
Age (years)	48.2 (13.3)	49.0 (13.4)	45.6 (13.1)	56.2 (12.8)
Sex				
Male	36 (50.7%)	31 (56.4%)	5 (31.3%)	8 (57.1%)
Female	35 (49.3%)	24 (43.6%)	11 (68.8%)	6 (42.9%)
BMI (kg/m²)	25.5 (4.1)	25.8 (3.8)	24.5 (4.8)	28.2 (4.7)
Duration of AI (years)	16.7 (11.0)	17.5 (11.0)	14.0 (11.0)	20.3 (12.7)
Diabetes mellitus	14 (19.7%)	11 (20.0%)	3 (18.8%)	14 (100.0%)
Hypertension	16 (22.5%)	14 (25.5%)	2 (12.5%)	7 (50.0%)

AI, adrenal insufficiency; BMI, body mass index; DM, diabetes mellitus. Results are presented as n (%) for categorical variables and mean (SD) for continuous variables. Percentages are based on the number of patients with non-missing values. [a]Randomized crossover plus 6-month extension study; [b]diabetes during randomized crossover plus 6-month extension study.

- The most common AEs were nasopharyngitis (70.4%), fatigue (52.1%) and gastroenteritis (47.9%); most AEs (84.8%) were unrelated to DR-HC.
- There were 65 serious AEs in 32 patients (19.8 per 100 patient-years); four were possibly related to DR-HC: acute AI (n = 2), gastritis (n = 1) and syncope (n = 1).
- Two deaths were reported (fall from height, subarachnoid haemorrhage), both classified as unrelated to DR-HC.

Intercurrent illness and increased hydrocortisone use

- Over the 5-year study, there were 709 episodes of intercurrent illness in 64 patients and 984 episodes of increased hydrocortisone use not due to intercurrent illness in 43 patients (Table 2).

Cardiometabolic parameters and vital signs

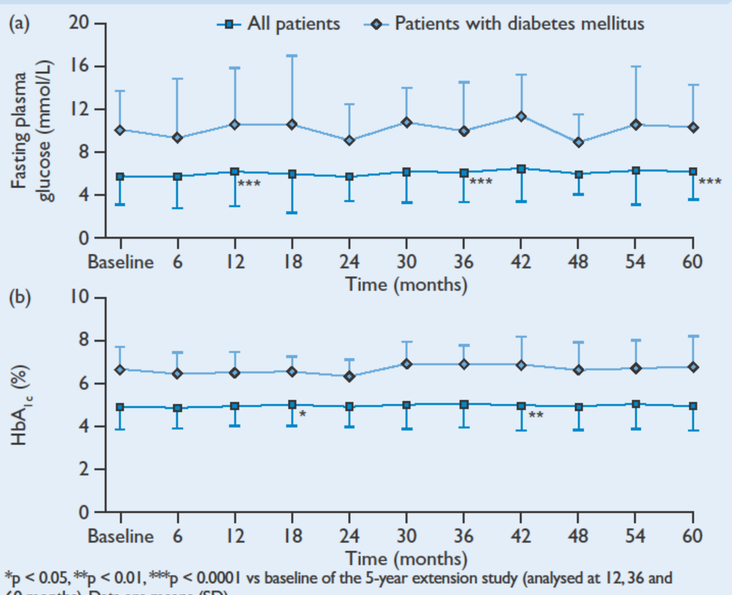
- Small but significant increases from baseline in the 5-year extension study were observed at all time points for mean fasting plasma glucose (Figure 2a) and at 12 and 36 months for mean HbA_{1c} (Figure 2b) in the overall safety population.
- Mean HDL-cholesterol was significantly increased at all time points in the overall safety population and at 36 and 60 months in patients with DM (Figure 3). Other lipid parameters were similar at baseline and 5 years in the overall safety population and in patients with DM.
- There were no statistically significant changes in vital signs, body weight or body mass index.

Table 2. Episodes of intercurrent illness and increased hydrocortisone use not due to intercurrent illness, over time.

	0–12 months (n = 71)	12–24 months (n = 68)	24–36 months (n = 68)	36–48 months (n = 67)	48–60 months (n = 67)	0–60 months (n = 71)
Intercurrent illness						
Episodes per patient	2.93 (3.86)	3.38 (5.05)	5.42 (16.73)	3.83 (9.63)	2.64 (3.41)	11.08 (23.81)
Days per episode	6.52 (19.70)	8.26 (19.07)	3.78 (2.76)	9.10 (28.40)	2.60 (2.64)	4.70 (8.16)
Dose per episode (mg)	19.16 (11.39)	18.92 (12.13)	23.47 (13.87)	18.65 (8.88)	19.12 (13.07)	20.48 (11.15)
Increased hydrocortisone use not due to intercurrent illness						
Episodes per patient	6.15 (8.72)	10.00 (14.97)	7.57 (9.11)	10.43 (16.31)	5.37 (7.69)	22.88 (33.53)
Days per episode	2.11 (2.06)	1.83 (1.27)	3.37 (6.57)	4.56 (10.90)	5.34 (14.14)	2.15 (1.58)
Dose per episode (mg)	15.26 (10.52)	15.49 (14.99)	14.62 (12.33)	13.36 (9.57)	14.53 (10.33)	15.48 (9.60)

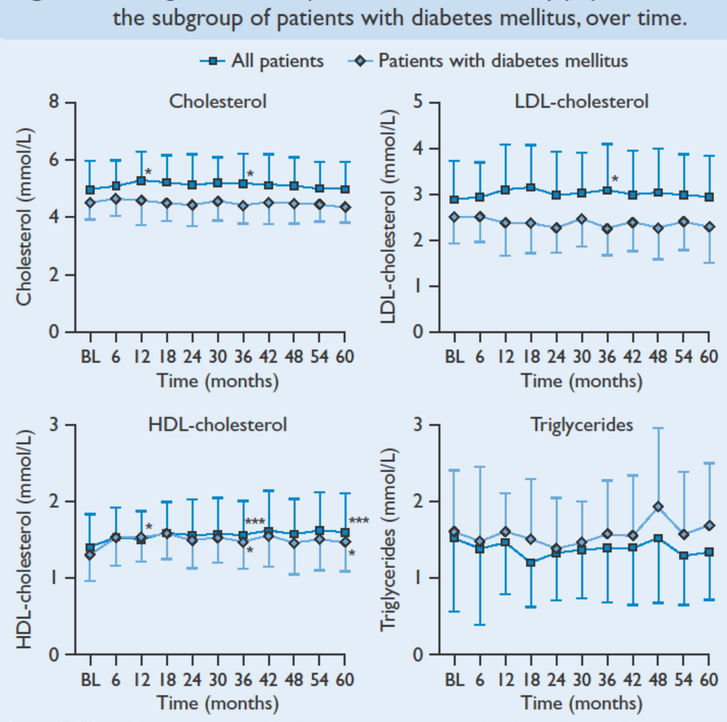
Data are presented as mean (SD). Mean values do not always consist of 0–60 month values because episodes of extra hydrocortisone use may have overlapped consecutive 12-month periods.

Figure 2. Changes in (a) fasting plasma glucose and (b) HbA_{1c} for the overall safety population and the subgroup of patients with diabetes mellitus, over time.



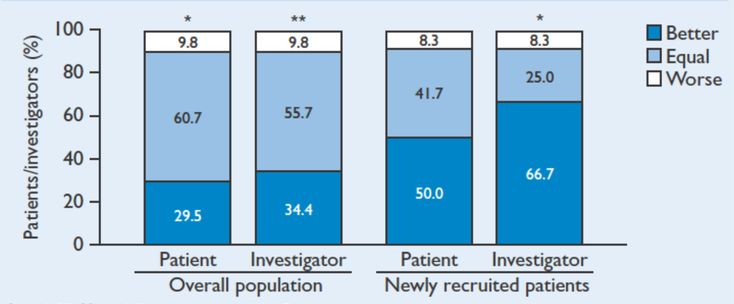
*p < 0.05, **p < 0.01, ***p < 0.0001 vs baseline of the 5-year extension study (analysed at 12, 36 and 60 months). Data are means (SD).

Figure 3. Changes in serum lipids for the overall safety population and the subgroup of patients with diabetes mellitus, over time.



*p < 0.05, ***p < 0.0001 vs baseline of the 5-year extension study (analysed at 12, 36 and 60 months). Data are means (SD).
BL, baseline; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Figure 4. Patient- and investigator-assessed tolerability (changes from baseline to 5 years).



*p < 0.05, **p < 0.01 vs baseline of the 5-year extension study.

Patient- and investigator-assessed tolerability

- Patient- and investigator-assessed treatment tolerability was significantly improved at 5 years versus baseline (Figure 4).

QoL

- There were no significant changes in FIS or PGWB total scores from baseline to 5 years. However, FIS physical functioning was significantly worse at 5 years (change from baseline: 1.8; p = 0.008), whereas PGWB scores numerically improved after 5 years.

CONCLUSIONS

- Long-term data demonstrate that the newly developed treatment option, DR-HC, is well tolerated with no safety concerns in patients with primary AI, including those with DM.
- The number of intercurrent illness episodes was similar for DR-HC and hydrocortisone three times daily in the randomized crossover plus 6-month extension study,[6] while intercurrent illness episodes and need for additional hydrocortisone remained stable over 5 years' DR-HC treatment.
- Patient- and investigator-assessed tolerability was significantly improved with long-term DR-HC treatment compared with baseline.
- The worsening of physical functioning over time reported here may reflect the decline in QoL commonly seen with ageing and with chronic diseases.[9]

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