Safety, Tolerability and Preliminary Signals of Activity in Adult Patients with Partly Controlled Asthma Treated with Live Biotherapeutic MRx-4DP0004 as an Add-on Maintenance Therapy to Inhaled Corticosteroids (ICS) with or without Long-acting beta agonists (LABA)

C. E. Brightling[1], L. Markinson[2], C. Moore[2], G. Dourado[2], C. Badham[2], A. Stevenson[2]

[1]University of Leicester, Maurice Shock Medical School, Leicester, United Kingdom, [2]4D pharma plc, Leeds, United Kingdom

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BACKGROUND

- The gut microbiome is known to be important for the development and proper functioning of the immune system and has been linked to various immune-mediated and atopic diseases.
- MRx-4DP0004 is a novel, gut microbiome-derived, oral, single strain Live Biotherapeutic Product (LBP) which reduced lung infiltration of neutrophils and eosinophils; infiltration and activation of dendritic cells; lung inflammatory scores; and tissue damage in animal models of severe asthma.
- MRx-4DP0004 is being evaluated as an add-on maintenance therapy in adults with partly controlled asthma in a two-part Phase I/II study (NCT03851250). Here we present safety and efficacy results from the completed Part A of this study.

METHODS

- A first-in-human, two-part Phase I/II, randomized, placebo-controlled clinical trial.
- In Part A, after a 2-week placebo run-in period, 34 patients with partly controlled asthma (1.5 ≥ ACQ-6 ≤ 4 at screening, and 1.0 ≥ ACQ-6 ≤ 4 at baseline) were randomized 1:1 to receive MRx-4DP0004 2 capsules PO BID ($1x10^9$ to $1x10^{10}$ CFU) or placebo, in addition to their regular maintenance asthma medication of inhaled corticosteroid (ICS) with or without long-acting β-agonist (LABA) for up to 12 weeks or until withdrawal.
- The primary endpoint of Part A was safety and tolerability.
- Secondary endpoints were related to asthma control (ACQ-6, AQLQ, SABA use) and exacerbations. The proportion of patients with a decrease in ACQ-6 from baseline will be the primary endpoint of the planned Part B, and in Part A was assessed by a one-sided Fisher's exact test, p<0.1.
- Following successful completion of Part A, Part B will assess clinical and biomarker activity in up to 90 patients.

PATIENT CHARACTERISTICS

The study recruited adult male and female subjects aged 18-65 with documented history and diagnosis of asthma for ≥6 months, stable asthma treatment per GINA 2020 steps 2-4 (ICS +/- LABA), ACQ-6 score >1.5 and ≤4, and FEV1 >50% of predicted normal.

There were no significant differences between MRx-4DP0004 and placebo arms at baseline.

	MRx-4DP0004	Placebo
Female (%) [1]	44.4%	18.8%
Age [1]	42.6 (13.57)	50.7 (9.83)
Baseline ACQ-6 score [1]	2.13 (0.70)	2.19 (0.51)
Baseline AQLQ score [1]	4.97 (1.01)	4.81 (0.79)
Baseline no. SABA puffs per week [2]	11.86 (7.51)	15.70 (16.26)
Baseline FEV1 (L) [2]	3.04 (0.89)	3.10 (0.79)
Baseline FVC (L) [2]	4.14 (1.00)	4.43 (0.89)
Baseline PEF (L/min) [2]	535.9 (115.05)	500.5 (135.70)
Baseline FeNO (ppb) [2]	38.16 (28.78)	25.88 (16.60)

Table 1, Patient characteristics. *[1] Full Analysis Set (FAS), all patients randomized, N=34; [2] Per Protocol Analysis Set (PPAS), all patients randomized without major protocol deviations, N=29; all figures are mean (± SD) unless otherwise stated.*

RESULTS - EFFICACY

1) **ACQ-6.** At all time points, a significantly greater proportion of patients receiving MRx-4DP0004 than those receiving placebo experienced a reduction in Asthma Control Questionnaire (ACQ-6) scores from baseline. This is the primary efficacy endpoint for Part B of this Phase I/II trial.
   - The proportion of patients with improved ACQ-6 increased over the treatment period
   - In addition, at all time points a greater proportion of MRx-4DP0004-treated patients experienced a decrease in ACQ-6 from baseline of ≥0.5, 50% vs 37.5% at end of treatment at D85.

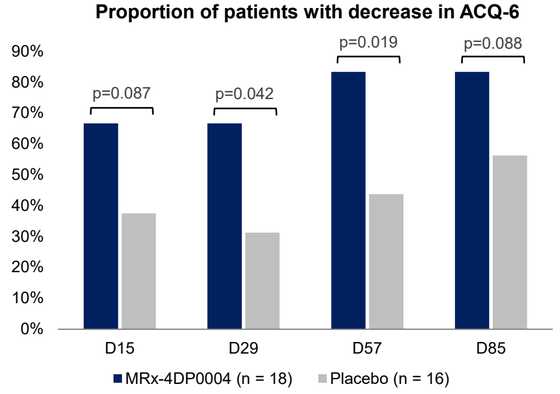

Figure 1. *Proportion of patients who experienced a decrease in ACQ-6 score from baseline at each time point. P values from one-sided Fisher's exact test, p<0.1.*

2) **Use of rescue medication.** At all time points a greater proportion of the MRx-4DP0004 arm than placebo arm reduced their total weekly use of SABA rescue medication.
   - At end of treatment on D85, 50% of patients receiving MRx-4DP0004 reduced their use of SABA compared to 18.8% for placebo.
   - Reliance on SABA rescue medication continued to decrease over the treatment period for MRx-4DP0004 treated patients, but this was not observed for placebo-treated patients.

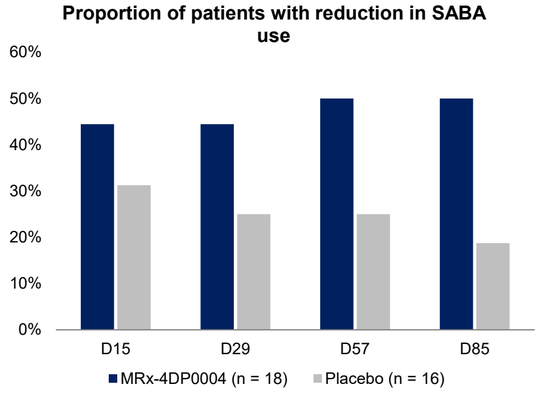

Figure 2. *Proportion of patients who reduced their weekly use of SABA rescue medication (puffs per week) compared to baseline.*

3) **AQLQ.** At end of treatment on D85, 50% of patients receiving MRx-4DP0004 had improved their Asthma Quality of Life Questionnaire (AQLQ) score by ≥0.5 from baseline, compared to 31.3% receiving placebo.

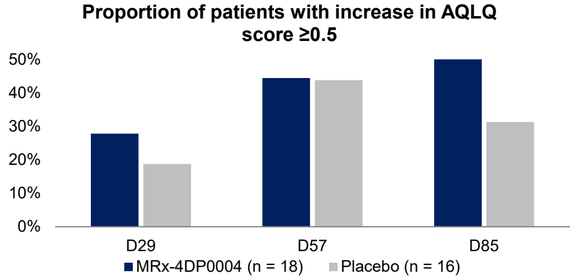

Figure 3. *Proportion of patients with an increase in AQLQ score of ≥0.5 compared to baseline at each time point. AQLQ score was not recorded on D15.*

4) **Exacerbations.** In the 12-week treatment period, there was one asthma exacerbation in the MRx-4DP0004 treatment arm, compared to two in the placebo arm. There were no exacerbations requiring hospitalization in either treatment arm.

5) **Lung function.** Mean measures of lung function – forced expiratory volume (FEV1), ratio FEV1:FVC (forced vital capacity), and peak expiratory flow (PEF) – remained within normal expected ranges from baseline and throughout the treatment period.

RESULTS - SAFETY

MRx-4DP0004 demonstrated a safety profile comparable to placebo.

- Frequency of adverse events (AEs) comparable to placebo.
- No treatment-related severe AEs or serious AEs reported.
- The only AE occurring in >1 patient and at greater frequency in MRx-4DP0004 than placebo arms was headache (N=3 vs placebo N=2).
- Data was reviewed by an Independent Data Monitoring Committee who recommended the study could progress to Part B.

	MRx-4DP0004 N (%)	Placebo N (%)
Subjects	18	16
All AEs	16	20
- Mild	10	16
- Moderate	6	4
- Severe	0	0
Treatment-related AEs	2	2
AEs leading to discontinuation	2 (11.1%)	2 (12.5%)
Serious AEs	0	0

Table 2, Summary of AEs. *All patients that received ≥1 dose MRx-4DP0004 or placebo.*

CONCLUSIONS

- MRx-4DP0004 is a potential novel oral immunomodulator asthma therapy that is safe and well-tolerated in asthma patients in addition to ICS ± LABA.
- Part A of this first-in-human study generated preliminary signals of clinical activity compared to placebo, with regards to improved asthma control and quality of life.
- To our knowledge these results are the first clinical evidence for a Live Biotherapeutic as a potential treatment for asthma.
- The study will now progress into Part B which will assess clinical and biomarker activity in up to 90 patients.
- The primary endpoint for Part B will be the proportion of patients with a reduction in ACQ-6 from baseline vs placebo, which was statistically significant at all time points in Part A.
- Part B is expected to enroll more symptomatic patients.

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