

Long-term budesonide treatment of collagenous colitis: a randomised, double-blind, placebo-controlled trial

O K Bonderup,¹ J B Hansen,² P S Teglbjærg,³ L A Christensen,⁴ J F Fallingborg²

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¹ Department of Internal Medicine, Randers Regional Hospital, Randers, Denmark;

² Department of Gastroenterology, Aalborg Hospital, Aalborg, Denmark;

³ Institute of Pathology, Aalborg Hospital, Aalborg, Denmark;

⁴ Department of Gastroenterology, Århus Hospital, Århus, Denmark

Correspondence to:
Dr O K Bonderup, Department of Internal Medicine, Randers Regional Hospital, Skovlyvej 1, 8900 Randers, Denmark; obo@rc.aaa.dk

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ABSTRACT

Objective: To evaluate the efficacy and safety of long-term budesonide therapy for the maintenance of clinical remission in patients with collagenous colitis.

Design: Randomised, placebo-controlled study with a 24-week, blinded follow-up period without any treatment.

Setting: Three gastroenterology clinics in Denmark.

Patients: Forty-two patients with histologically confirmed collagenous colitis and diarrhoea (more than three stools/day).

Interventions: Patients in clinical remission after 6 weeks' open-label therapy with oral budesonide (Entocort CIR capsules, 9 mg/day) received 24 weeks' double-blind maintenance therapy with budesonide 6 mg/day or placebo. Thereafter, patients entered the 24-week, blinded follow-up period.

Main Outcome Measure: The proportion of patients in clinical remission (three or fewer stools/day) at the end of maintenance therapy.

Findings: A total of 34 patients in remission at week 6 were randomly assigned to budesonide 6 mg/day (n = 17) or placebo (n = 17). After 24 weeks' maintenance treatment, the proportions of patients in clinical remission were 76.5% (13 of 17) with budesonide and 12% (2 of 17) with placebo (p < 0.001). At 48 weeks (the end of the follow-up period, without any treatment) these values were 23.5% (4 of 17) and 12% (2 of 17), respectively (p = 0.6). The median times to relapse after stopping active treatment (6 plus 24 weeks in the budesonide group; 6 weeks in the placebo group) were 39 and 38 days, respectively. Long-term treatment with budesonide was well tolerated.

Conclusions: Long-term maintenance therapy with oral budesonide is efficacious and well tolerated for preventing relapse in patients with collagenous colitis. The risk of relapse after 24 weeks' maintenance treatment is similar to that observed after 6 weeks' induction therapy.

Together with lymphocytic colitis, collagenous colitis is a subtype of "microscopic colitis".^{1,2} By definition, therefore, the mucosa of the colon is often macroscopically normal upon colonoscopy and biopsies from the rectal or colonic mucosa are necessary in order to make a diagnosis. Collagenous colitis is characterised histologically by mucosal lymphocytic inflammation and an abnormal thickening of the subepithelial collagen layer (typically >10 µm) in the colon.^{1,2}

Clinically, the primary symptom of collagenous colitis is chronic watery diarrhoea; abdominal pain and distension and weight loss may also be present.¹ In most patients the course is typically benign.² It is estimated to be diagnosed in up to six

cases per 100 000 persons per year and is most common among women in their 50s and 60s.²⁻⁵ The precise aetiology of the disease is uncertain, although associations have been proposed with autoimmune diseases, toxins in the faecal stream and the use of certain drugs, including non-steroidal anti-inflammatory drugs.^{2,6,7}

Budesonide is a corticosteroid that is commonly used to treat chronic inflammatory conditions of the lower gastrointestinal tract. It has a potent local anti-inflammatory effect because of its high affinity for glucocorticoid receptors in the gut. Coupled with almost complete first-pass metabolism in the liver, leading to low systemic exposure, it has favourable tolerability when administered by mouth.⁸ After preliminary indications of therapeutic potential,⁹ the efficacy and tolerability of oral budesonide for the induction of remission of collagenous colitis has been confirmed in a number of randomised, placebo-controlled studies.¹⁰⁻¹³ Indeed, treatment with budesonide 9 mg/day for up to 8 weeks achieved clinical remission in a significantly greater proportion of patients compared with placebo. A Cochrane review revealed the number needed to treat for clinical response to be two patients.¹⁴ Long-term (maintenance) therapy with oral budesonide is well tolerated and effective for maintaining clinical remission.¹⁵ The recent MIMIC study,¹⁶ for example, reported that almost all (87%) budesonide recipients remained in clinical remission after 6 months' maintenance therapy compared with only 39% of placebo recipients. However, there remains a high risk of clinical relapse after stopping maintenance therapy with oral budesonide,^{17,18} and there is currently a lack of prospective data in this setting.

The aim of this study was to evaluate the clinical and histological effects of long-term treatment with oral budesonide (Entocort CIR capsules) after successful induction therapy in patients with collagenous colitis and whether a risk of relapse remains after stopping long-term treatment.

METHODS

Study design

This was a randomised, double-blind, placebo-controlled, multicentre study (ClinicalTrials.gov identifier: NCT00139162; COLIT) in male and female patients aged 18 years and older with histologically confirmed collagenous colitis, ie, diffuse lymphocytic inflammation and evidence of a collagenous band greater than 10 µm, at least focally upon colorectal mucosal biopsy. Patients were required to have diarrhoea (mean stool

frequency of more than three per day over three consecutive days) plus negative faecal cultures for intestinal pathogens. Patients treated with salazopyrine, 5-aminosalicylic acid, budesonide or a systemic glucocorticoid during the past 3 months were excluded, as were those treated with ketoconazole during the 7 days before random selection. Patients with other chronic gastrointestinal diseases (including coeliac disease), clinically relevant impairment of kidney or liver function, previous intestinal resection or stoma were also excluded. The study was carried out with approval from the Ethical Committee of Århus County, the Danish Health Agency and Data Protection Agency, and in accordance with the Declaration of Helsinki and Good Clinical Practice principles. All patients provided written informed consent not only to participate in the study but also to subsequent publication of the study findings in an international journal.

During an initial, 6-week, open-label induction phase (fig 1), eligible patients received oral budesonide 9 mg once a day (3×3 mg capsules; Entocort CIR capsules; AstraZeneca, Lund, Sweden). Those with clinical remission (mean stool frequency of three or fewer per day) were randomly assigned to 24 weeks' double-blind treatment with budesonide 6 mg once a day (2×3 mg capsules) or matching placebo, after which patients entered a 24-week, blinded follow-up period (the randomisation code was unbroken until completion of follow-up, such that neither patients nor physicians knew which treatment the patient had received during maintenance therapy). Computer-generated block randomisation was performed to ensure that each centre allocated the same number of patients. Those patients with relapse during the maintenance or follow-up periods were offered treatment with open-label budesonide (9 mg once a day for 6 weeks, followed by budesonide 6 mg once a day for 24 weeks).

Efficacy assessments

Mean stool frequency during three consecutive days was recorded every fourth week during the maintenance and follow-up periods, and the mean of the three values was recorded. Clinical relapse was defined as more than three stools per day. Faecal weight (g/day, collected for three consecutive days) was also recorded.

Histology

Colonoscopy or sigmoidoscopy was performed at baseline and at the end of the maintenance period and involved examination of at least 40 cm of the colon. Standardised biopsies were obtained from every 7 cm of the colon (six biopsies in total per examination). For histological assessment, sections from each biopsy were prepared and stained with haematoxylin-eosin and Masson-Trichrome. Histological sections at right angles to the

mucosal surface were secured. The thickness of the collagen layer was measured at 10 points at a magnification of 600 on a monitor screen. The first measuring point was randomly chosen, the other nine were placed at fixed intervals of $166.67 \mu\text{m}$ (10 cm on the screen) from the first point to avoid selection bias (so-called "systematically random sampling").¹⁹ This procedure was performed at four biopsy levels from the colon 20 cm to at least 40 cm from the anal verge. The average thickness of the collagen layer was then calculated. Biopsies from the rectum, ie, 7 cm and 14 cm from the anal verge, were disregarded. The degree of inflammation was assessed on a 4-point scale on which 0 was absent and 3 was severe.¹² All histological assessments were performed by one author (PST), who was blinded to the treatment groups and the treatment response.

Safety assessments

Adverse events were recorded at each clinic visit by the investigator and evaluated in terms of severity and causality. Laboratory tests (haematology, biochemistry) were also performed at each clinic visit.

Statistical methods

The primary variable was the proportion of patients who remained in clinical remission at the end of the 24-week maintenance period. Secondary variables included time from the end of active treatment to clinical relapse and change in histological appearance (based on the degree of inflammation and the thickness of the collagen layer). All analyses were completed on an intention-to-treat basis; premature discontinuation of treatment was considered as relapse in both treatment arms.

The sample size estimate was based on a minimum difference between treatment groups of 50%, ie, an expected remission rate of 80% after 24 weeks of active treatment and a placebo effect of 30%.¹⁴ With a type I error risk of 5% and power of 80%, it was estimated that 18 patients would be required in each treatment arm (ie, a total of 36 patients). Assuming a remission rate of 80% and a dropout rate of 10% during the 6-week induction treatment period, 51 patients would be required for this period. It was expected that 17 patients at each of the three centres would be enrolled, of which 12 would receive study drug, and of these five to six would continue to the 24-week treatment period. Therefore, approximately 15–18 patients were expected to enter the 24-week maintenance treatment period.

Time to relapse was analysed for the intention-to-treat population using Kaplan-Meier estimates and the Mantel-Haenszel log-rank test. Between-group differences in the rates of relapse at weeks 24 and 48 were analysed using Fishers' exact

Figure 1 Study design.

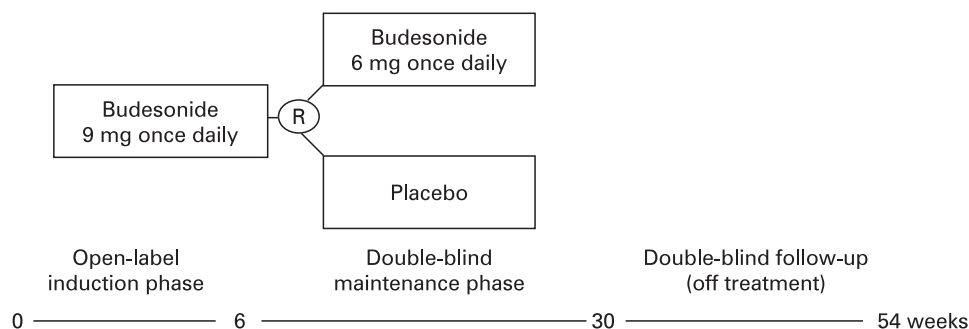
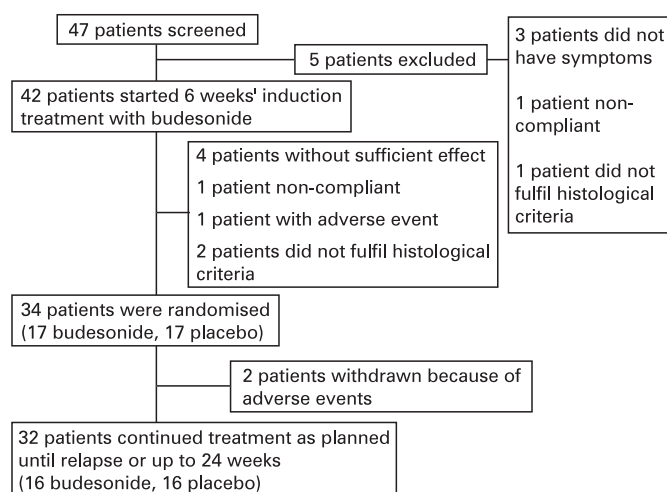


Figure 2 Flow of patients through the study.

test. The Wilcoxon test for pair differences was used to analyse between-group differences in histological variables (collagen layer thickness and grade of inflammation). Safety data were analysed descriptively.

RESULTS

The flow of patients through the study is depicted in fig 2; the first patient entered the study on 9 August 2004 and the final patient completed the study on 8 February 2007. A total of 42 patients commenced open-label induction therapy with budesonide 9 mg once a day (most patients were newly diagnosed and had not previously been treated with budesonide or other steroids; three patients had previously been treated with budesonide). Of these, four patients had an insufficient response, one patient was non-compliant and three patients were withdrawn because they did not fulfil the histological criteria ($n = 2$) or had an adverse event ($n = 1$). Therefore, 34 patients entered the 24-week maintenance treatment phase and were randomly assigned to budesonide 6 mg once a day ($n = 17$) or placebo ($n = 17$). Baseline demographic and clinical characteristics were similar between the two treatment groups, with the exception that the budesonide group contained a lower proportion of female patients (table 1). Two patients, one in each group, discontinued maintenance treatment because of adverse events. The remaining patients continued treatment as planned until relapse or up to 24 weeks. There were no drop-outs in the follow-up period.

Efficacy findings

After 24 weeks' maintenance treatment, 13 of 17 patients (76.5%) in the budesonide group and two of 17 patients (12%) in the placebo group remained in clinical remission ($p < 0.001$). At the end of 24 weeks' blinded follow-up, these values were four (23.5%) and two (12%), respectively ($p = 0.6$) (fig 3). Further analysis showed that the six patients who remained in clinical remission at the end of 24 weeks' follow-up did not differ from the overall study population in terms of age, gender or concomitant medication.

The median time to relapse after the end of the 6-week treatment period was 199 days (range 6–297) in the budesonide group versus 38 days (range 1–138) in the placebo group ($p < 0.02$). In contrast, the median time to relapse after stopping active treatment (ie, 6 plus 24 weeks in the budesonide group versus 6 weeks in the placebo group) was 39 days (range 6–129) and 38 days (range 1–138), respectively ($p = 0.35$).

Colonoscopy or sigmoidoscopy with biopsy was performed at baseline in all 34 patients who entered the long-term treatment phase. At relapse or at the end of the maintenance phase, repeat endoscopy with biopsy was performed in 21 patients. Among evaluable patients, those treated with budesonide ($n = 10$, including two patients with relapse of symptoms) showed a significant improvement from baseline in mean thickness of the collagen layer (9.7 μm versus 23.8 μm ; fig 4) and the mean degree of inflammation (0.9 versus 2.4; fig 5) (both $p < 0.01$). No significant improvements from baseline in these variables were observed with placebo ($n = 11$), most biopsies having been

Table 1 Baseline demographic and clinical characteristics of the study population who entered the maintenance treatment phase ($n = 34$)

	Budesonide ($n = 17$)		Placebo ($n = 17$)	
Sex	11 women;	6 men	16 women;	1 man
Mean age, years (range)	62.8 (42–81)		58.4 (33–82)	
Mean stool frequency, number/day (range)				
Baseline	5.9 (3.3–8.7)		6.7 (3.3–11.3)	
Week 6*	1.5 (0.3–2.7)		1.7 (0.7–2.7)	
Mean stool weight, g/day (range)				
Baseline	599 (224–1655) ($n = 13$)		522 (311–869)	
Week 6*	160 (61–343) ($n = 11$)		173 (53–372) ($n = 14$)	

*Start of maintenance treatment phase.

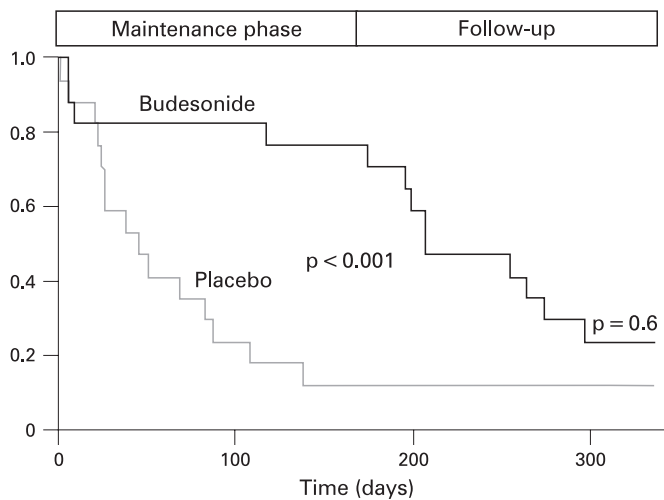


Figure 3 Kaplan-Meier curves of relapse-free survival during maintenance and follow-up (untreated); p values correspond to the between-group difference at the end of maintenance and follow-up, respectively.

taken from patients at relapse ($n = 9$) (fig 4). Irrespective of treatment, the 10 patients in remission at repeat colonoscopy (budesonide, $n = 8$; placebo, $n = 2$) had a decreased mean thickness of the collagen layer ($7.0 \mu\text{m}$ versus $18.31 \mu\text{m}$) and a lower degree of inflammation (0.4 versus 2.4) compared with the 11 patients for whom biopsies were taken at the time of relapse (budesonide, $n = 2$; placebo, $n = 9$).

Tolerability

Treatment with budesonide was well tolerated, and most adverse events were mild and transient in nature. During the 6-week induction period, a total of 12 patients (29%) reported 12 adverse events, the most common of which were leg cramps (four reports), dyspepsia (three) and oedema (two). One patient discontinued from the study due to leg cramps, which resolved after treatment cessation; the relationship to study medication was uncertain.

During the 24-week maintenance period, a total of five patients (29%) in the budesonide arm and eight patients (47%) who received placebo reported five and eight adverse events, respectively. Among budesonide recipients, adverse events included worsening of diabetes (two reports), dyspepsia (one), bruising (one) and subarachnoid haemorrhage (one). The latter adverse event, which occurred after 22 weeks' active treatment (ie, 6 weeks' induction plus 16 weeks' maintenance therapy), was considered to be serious and the patient was withdrawn from the study. The event was not deemed to be drug related and the patient ultimately recovered with minor sequelae. Among placebo recipients, adverse events included dyspepsia (three reports), leg cramps (two), bruising (one), headache (one) and depression (one). The patient who experienced depression (which was not deemed to be drug related) was discontinued from the study.

There were no clinically relevant trends with regard to changes in laboratory tests during the study.

DISCUSSION

This study, which was designed to mirror routine clinical practice for the management of patients with collagenous colitis, confirms that oral budesonide is efficacious for the

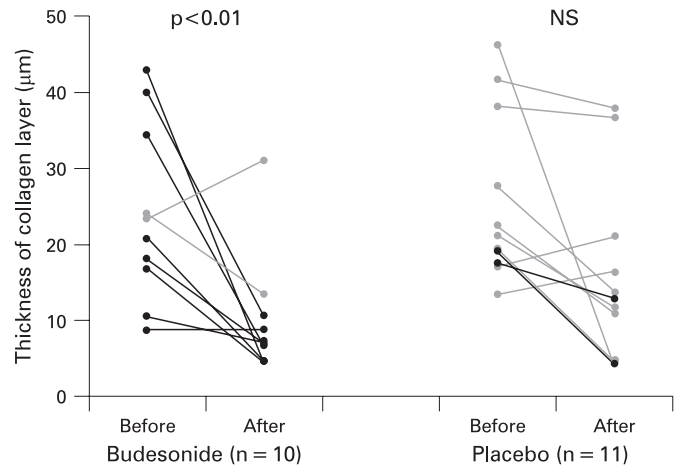


Figure 4 Collagen layer thickness at baseline and after treatment with oral budesonide or placebo in patients with collagenous colitis (biopsies after treatment were taken at relapse or at termination of 24 weeks' maintenance therapy). NS, not significant. Overlapping lines for some patients; grey lines indicate patients for whom biopsies were taken at relapse.

induction of clinical remission in patients with collagenous colitis. Such findings support the conclusions of the recent Cochrane review of randomised trials in collagenous colitis, which indicated that budesonide is the only treatment for which there is strong evidence of a clinical benefit for the induction of clinical remission.¹⁴ Importantly, the present study also confirms the efficacy and favourable tolerability of budesonide for the long-term maintenance of clinical remission (which was paralleled by histological improvement), in accordance with the findings of the MIMIC study.¹⁶ Taken together, such results are important given the paucity of published data on the long-term use of oral budesonide or other treatments in the setting of collagenous colitis.^{2 14}

Whereas the present study confirms the efficacy of budesonide for the induction and maintenance of clinical remission in

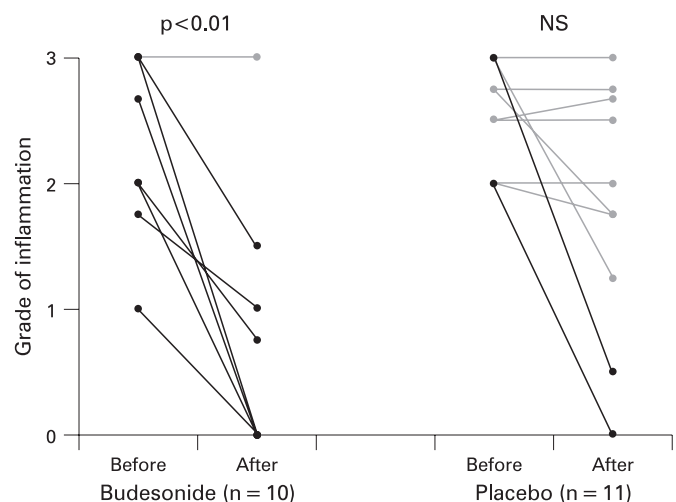


Figure 5 Grade of inflammation at baseline and after treatment with oral budesonide or placebo in patients with collagenous colitis (biopsies after treatment were taken at relapse or at termination of 24 weeks' maintenance therapy). NS, not significant. Overlapping lines for some patients; grey lines indicate patients for whom biopsies were taken at relapse.

patients with collagenous colitis, it also shows that the risk of relapse returns after such therapy is discontinued. Indeed, the majority of patients had relapsed within 6 months (more than half within 40 days). Such findings, based on a blinded follow-up period, are consistent with those of previous studies demonstrating the risk of relapse after stopping treatment with oral budesonide.^{17 18} Whereas the relapse-free survival curve showed some post-treatment effect with budesonide, this was relatively transient and the underlying mechanism of action remains unclear. It also has to be considered that the aetiology and exact pathogenesis of the disease is unknown, such that the disease may relapse sooner or later after the cessation of therapy irrespective of the pharmacological mechanism of action.

The selection of the budesonide dose for the induction of clinical remission was based on previous studies in which budesonide 9 mg/day was shown to be optimal in terms of the treatment of patients with collagenous colitis.^{9–13} The maintenance dose was selected on the basis of previous studies of budesonide for maintenance therapy in patients with Crohn's disease, which have demonstrated that budesonide 6 mg/day for up to 12 months was both well tolerated and efficacious for maintaining clinical remission.^{20–22}

In addition to its double-blind, placebo-controlled design and a blinded, untreated follow-up period, another strength of this study was the inclusion of histological outcomes. This was deemed important given the need to demonstrate both histological and clinical remission during treatment for collagenous colitis.¹⁴ Indeed, it was noted that the efficacy of budesonide for long-term maintenance of clinical remission was paralleled by significant histological improvement compared with placebo, although the fact that not all patients were evaluable for histology upon relapse or completion of maintenance therapy means that our findings may not be representative of the entire patient population.

An interesting finding of the present study was the trend towards histological improvement among the small number of placebo patients who remained in remission during maintenance therapy. This finding exemplifies the relationship between symptoms and a possible inflammatory aetiology and undoubtedly reflects the chronic clinical course of collagenous colitis, which shows a variable course of symptoms during long-term follow-up.²³

Given the chronic nature of collagenous colitis, a need exists for prolonged, well-tolerated therapy to prevent relapse. In this regard, the risk of steroid-related adverse events with long-term budesonide treatment is an important consideration. However, consistent with other studies of long-term budesonide therapy in patients with chronic inflammatory bowel diseases,^{20–22} budesonide was well tolerated in this study and no serious adverse events related to study medication were reported. Although alternative long-term treatments have been described, including immunosuppressive therapies,^{24 25} no controlled studies have been performed.

CONCLUSIONS

Long-term maintenance therapy with oral budesonide is efficacious and well tolerated for preventing clinical relapse in patients with collagenous colitis. However, the risk of relapse after 24 weeks' maintenance treatment is similar to that observed after 6 weeks' induction therapy.

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Competing interests: None.

Ethics approval: The study was carried out with approval from the Ethical Committee of Århus County, the Danish Health Agency and Data Protection Agency, and in accordance with the Declaration of Helsinki and Good Clinical Practice principles.

Patient consent: Obtained.

Contributors: The study was planned and designed by OKB. Data collection and analysis was performed by the authors, who took final responsibility for manuscript content and the decision to submit for publication. All authors contributed to the interpretation of the study findings and in the writing of the manuscript. Medical writing support was provided by Steve Winter, from Wolters Kluwer Health (Chester, UK), with funding from AstraZeneca.

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