# SUMMARY

**ASTRAZENECA**

**FINISHED PRODUCT:** ACCOLATE™

**ACTIVE INGREDIENT:** Zafirlukast

**Trial title (number):** A Multicentre, Open-label, Long-term Safety Trial of ACCOLATE™ (20 mg bd) in Participants from Earlier ACCOLATE Clinical Trials (9188IL/0137).

**Clinical phase:** IIIb

**First patient recruited:** 8 July 1996
**Last patient completed:** 7 October 1999
**AstraZeneca approval date:** 25 September 2000

**Principal investigator and location (centre number)**: Not applicable for this trial.

**Publications:** None at the time of writing this report.

**OBJECTIVE:** To assess the safety of zafirlukast (20 mg bd) when taken for a period of up to 2 years by asthmatic patients.

**METHODS**

**Design:** This trial was a multicentre, open-label trial in asthmatic patients who had successfully completed a previous trial with zafirlukast that began in or after 1995. All such patients were eligible, irrespective of whether they had received zafirlukast, another asthma therapy, or placebo in the earlier trial. It was expected that most patients would enter the trial directly at Visit 2 (Week 0), as soon as blood results from their final visit of the previous zafirlukast trial were available. If however, there was a break in zafirlukast trial treatment of more than 2 weeks before entry into this trial, then these patients were re-assessed at a screening visit (Visit 1 Week -1]). Further assessments were carried out at entry to the treatment period (Visit 2 [Week 0]); at Visit 3 (Week 4); at Visit 4, [Week 13]); and then every 13 weeks thereafter (Visit 5 [Week 26], etc), up to and including Visit 11 (Week 104).

Under the original protocolled trial design, those patients who had never received zafirlukast before were to attend an additional clinical visit at Visit 3 (Week 4), to assess any immediate effects of zafirlukast treatment. However, all patients, irrespective of whether they had/had not previously received zafirlukast, attended Visit 3 (Week 4) and followed the visit structure as described above.

**Population:** At least 100 but no more than 500 patients.

**Key inclusion criteria:** Completed a clinical trial of zafirlukast which had started in 1995 or later.

**Key exclusion criteria:** Hospitalisation (overnight admission) for asthma within the last 3 months before Visit 1 (Week -1); any significant respiratory disease, other than reversible airways obstruction; history of having taken barbiturates or other drugs affecting the liver drug-metabolising enzymes within 4 weeks before Visit 1 (Week -1). All the above exclusion criteria only applied to patients who had to attend the re-evaluation visit (Visit 1 [Week -1]).

**Dosage:** Zafirlukast 20 mg bd. Each zafirlukast 20-mg dose was comprised of 1 zafirlukast 20-mg tablet. Patients were required to take 1 tablet twice daily during the treatment period. Formulation and batch numbers were: zafirlukast 20 mg tablets, F7157 (batch numbers 28124/95 and 37409E96).

**Key assessments**

**Safety:** Assessed by the recording of adverse events, routine clinical laboratory tests and physical examinations. Patients were interviewed for subjective symptomatology and any adverse event details were collected. Data were listed and summarised without formal statistical analysis.

---

**RESULTS**

**Demography:** A total of 204 patients (90 male [44.1%], 114 female [55.9%]) entered the trial and received zafirlukast 20 mg bd. Their mean age was 41.1 years (range 12 to 72 years). Of these 204 patients, 17 (8.3%) were exposed for 6 months or less; 56 (27.5%) were exposed for between 6 to 12 months; 82 (40.2%) were exposed for between 12 to 24 months; and 49 (24.0%) were exposed for >24 months. The mean (SD) duration of trial treatment for all patients was 73.2 weeks (34.20); (range 0 to 166 weeks). This calculation excludes Patients 0014/0005 and 0775/0005 who had no treatment information as they were lost to follow up at Visit 3.

A total of 57 patients (27.9%) were withdrawn from the trial. Only 1 patient (0.5%) was withdrawn because of worsening asthma. The number of patients withdrawn due to other causes (eg, lost to follow up; protocol non-compliance; etc) was similar to each other.

**Safety:** Adverse events during trial treatment are summarised in Table I.

**Table I Overview of adverse events**

| Category[a] | Zafirlukast 20 mg bd | |
|---|---|---|
| | Number of adverse events | Number of patients (%) |
| Patients at risk | - | 204 (100.0) |
| All adverse events | 673 | 150 (73.5) |
| Adverse events associated with death | 0 | 0 (0) |
| Adverse events reported as serious[b] | | |
| not leading to withdrawal | 7 | 6 (2.9) |
| leading to withdrawal | 3 | 2 (1.0) |
| Other adverse events leading to withdrawal | | |
| not asthma exacerbation | 7 | 9 (4.4) |
| asthma exacerbation | 1 | 1 (0.5) |
| Other adverse events | 655 | 149 (73.0) |

[a] Adverse event categories are mutually exclusive: events are counted in 1 category only. Patient categories are not mutually exclusive; patients may have adverse events in more than 1 category.
[b] A serious adverse event was defined as an adverse event that: was fatal; was life-threatening; caused or prolonged hospitalisation; caused disability or incapacity; required medical intervention to prevent permanent impairment or damage, was a cancer, congenital abnormality or resulted from an overdose.

A total of 150 patients (73.5%) experienced at least 1 adverse event: 8 patients (3.9%) reported serious adverse events, 2 of which led to withdrawal of trial treatment; 10 patients (4.9%) had non-serious adverse events that led to withdrawal, only 1 of which was withdrawn due to an exacerbation of asthma. The most common adverse event during the trial was aggravation reaction (asthma exacerbation), with 56 patients (27.5%) reporting this type of event. Only 1 of these patients had an asthma exacerbation that was serious. Other commonly reported adverse events included pharyngitis (48 patients [23.5%]) and infection (38 patients [18.6%]).
Three patients had clinically relevant elevations in liver function parameters: 1 had elevated alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT) levels and bilirubinemia and was withdrawn; and 1 had elevated ALT/SGPT levels and was withdrawn. Events for both of these patients were considered to be related to trial treatment by the investigator. A further patient had elevated levels of alkaline phospatase, ALT/SGPT, AST/SGOT and gamma glutamal transferase at 1 visit which were not reported as adverse events. Values for all patients returned to within the reference ranges at follow-up visits. Mean eosinophil counts were reduced during the trial. However, the number of patients contributing to the mean also fell in parallel and so clinical interpretation of these data without a placebo comparator is limited.
There were no clinically relevant changes observed at the physical examination performed at the end of the trial, and few patients had a significant deterioration in their asthma during the trial.