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Safety, tolerability and lymphocyte-lowering properties of etrasimod (APD334), an oral, potent, next-generation, selective S1P receptor modulator, after dose escalation in healthy volunteers

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Conclusions

- Etrasimod was well tolerated at all single and multiple doses up to 3.0 mg. There were no clinically significant changes in ocular exams, liver and pulmonary function tests
- Treatment with etrasimod produces a dose-dependent, significant and sustained decrease in lymphocyte count with the 2.0 mg dose, with complete lymphocyte recovery after 7 days
- These results support the further clinical development of etrasimod in autoimmune and inflammatory diseases

Introduction

- Sphingosine-1-phosphate (S1P) is a membrane-derived lysophospholid signaling molecule involved in many physiological and pathophysiological processes[1,2]
- Non-selective S1P modulators have been associated with potentially serious adverse events (AEs)[3–5]
- Etrasimod is an oral, potent, next-generation S1P modulator with an optimised S1P receptor activity profile in Phase 2 clinical development for ulcerative colitis
- Etrasimod selectively targets S1P receptor subtypes 1, 4, and 5 to provide systemic and local immune cell modulation,[6] while potentially reducing immunosuppressive side effects and avoiding adverse side effects associated with subtypes 2 and 3[3–5]

Objectives

- To investigate safety, tolerability and pharmacodynamic properties of single and multiple ascending doses of etrasimod in healthy adults

Methods

- Two Phase I, randomised, double-blind studies evaluated safety and pharmacodynamics of etrasimod in:
  - Single-dose escalation study
    - 0.1, 0.35, 1.0, 3.0 or 5.0 mg (n=6 per cohort) or placebo (n=10)
  - Multiple ascending dose study (Figure 1)
    - 0.7, 1.35 or 2.0 mg (n=10 per cohort) or placebo (n=10); or
    - 2.0 or 3.0 mg in a one step dose titration scheme (n=10 per cohort), daily for 21 days
- Subjects included healthy adults (18–45 years; 50–100 kg) who were non-smokers and not taking prescription medications

Results

Single-dose escalation study

- All 40 subjects completed the study

Safety and tolerability:

- Etrasimod was well tolerated at doses ≤3.0 mg
- Most commonly reported AEs were headache (0.1 mg: 1/6; 0.35 mg: 1/6; 3.0 mg: 1/6; 5.0 mg: 3/6; placebo: 2/10) and contact dermatitis (0.35 mg: 1/6; 1.0 mg: 2/6; 3.0 mg:1/6; placebo: 2/10)
- In the highest dose, 5.0 mg:
  - One subject had asymptomatic first and second degree atrioventricular (AV) block with bradycardia
  - Two subjects had first degree AV block, one associated with bradycardia
- Further dose escalation was discontinued
- There were no serious AEs reported

Multiple ascending dose study

- 60 subjects were enrolled, 59 completed (1 withdrew consent for personal reasons)

Safety and tolerability:

- Etrasimod was well tolerated at all tested doses (non-titrated 0.7, 1.35; 2.0 mg as well as one-step titration from 0.35 to 2.0 and from 0.5 to 3.0 mg)
- AEs occurring in one or more subjects are shown in Table 1
  - Most AEs were mild and not dose-responsive (except leukopenia, which occurred only in the 0.5/3.0 mg dose group)
  - Three subjects developed first degree AV block defined as PR >200 ms: one subject in the placebo group, one in the 2.0 mg dose group and one in the 0.5/3.0 mg dose group
  - No second degree or higher AV block was observed
- There were no serious AEs reported; no discontinuations due to AE
- There were no clinically significant changes in ocular exams, liver and pulmonary function tests over 21 days of treatment

Pharmacodynamic responses

- Treatment with etrasimod produced a dose-dependent and sustained decrease in lymphocyte count, with potent lymphocyte-lowering at 2.0 mg (Figure 2)
- Etrasimod 2.0 mg reduced lymphocyte counts by 69% from baseline to day 21
- Lymphocyte counts returned to baseline within 7 days of discontinuation (Figure 2)

Figure 1. Multiple ascending dose study design

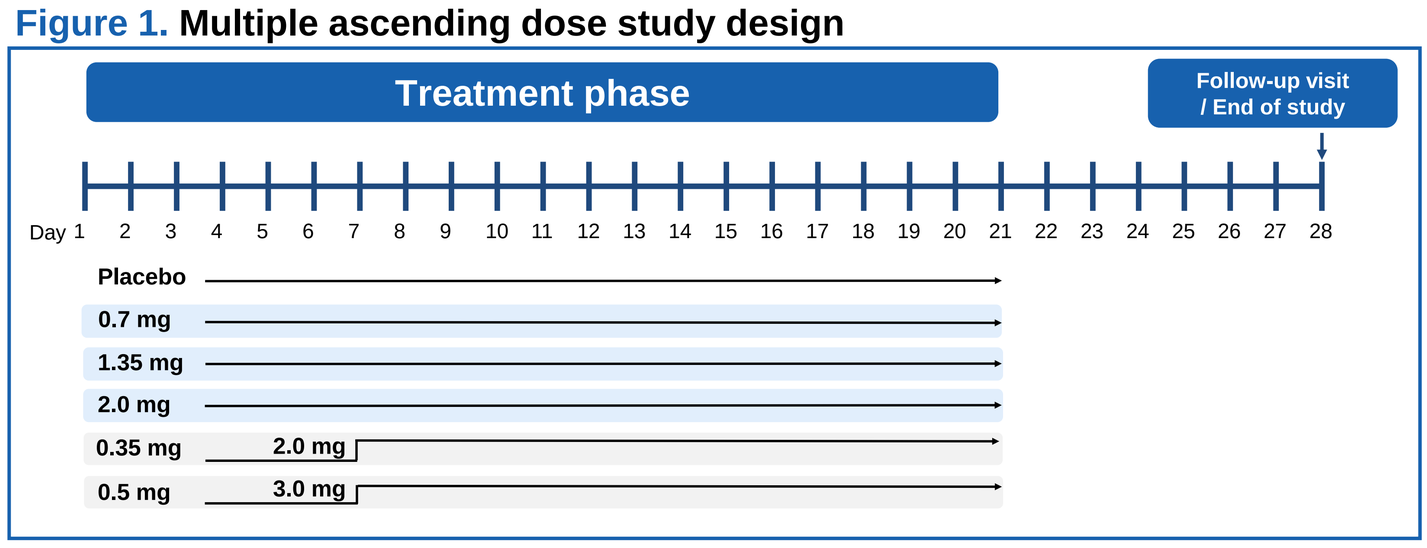
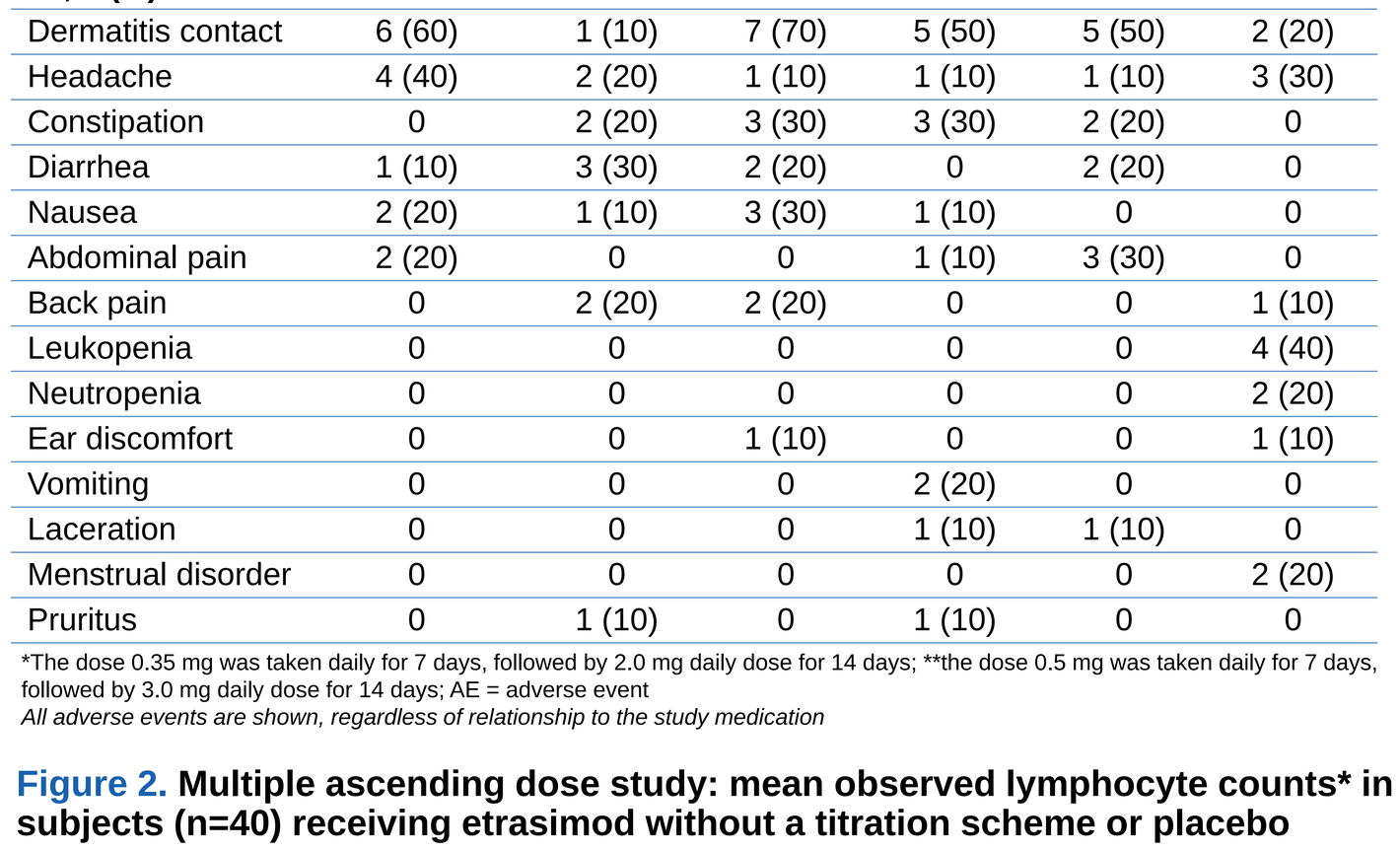


Table 1. Summary of treatment-emergent AEs reported by ≥1 subject (n=60) receiving etrasimod or placebo for 21 days in the multiple ascending dose study

Cohort	Placebo, once daily	Etrasimod once daily, mg				
Dose		0.7	1.35	2.0	0.35/2.0*	0.5/3.0**
Subject, n	**10**	**10**	**10**	**10**	**10**	**10**
AE, n (%)						
Dermatitis contact	6 (60)	1 (10)	7 (70)	5 (50)	5 (50)	2 (20)
Headache	4 (40)	2 (20)	1 (10)	1 (10)	1 (10)	3 (30)
Constipation	0	2 (20)	3 (30)	3 (30)	2 (20)	0
Diarrhea	1 (10)	3 (30)	2 (20)	0	2 (20)	0
Nausea	2 (20)	1 (10)	3 (30)	1 (10)	0	0
Abdominal pain	2 (20)	0	0	1 (10)	3 (30)	0
Back pain	0	2 (20)	2 (20)	0	0	1 (10)
Leukopenia	0	0	0	0	0	4 (40)
Neutropenia	0	0	0	0	0	2 (20)
Ear discomfort	0	0	1 (10)	0	0	1 (10)
Vomiting	0	0	0	2 (20)	0	0
Laceration	0	0	0	1 (10)	1 (10)	0
Menstrual disorder	0	0	0	0	0	2 (20)
Pruritus	0	1 (10)	0	1 (10)	0	0

*The dose 0.35 mg was taken daily for 7 days, followed by 2.0 mg daily dose for 14 days; **the dose 0.5 mg was taken daily for 7 days, followed by 3.0 mg daily dose for 14 days; AE = adverse event
All adverse events are shown, regardless of relationship to the study medication

Figure 2. Multiple ascending dose study: mean observed lymphocyte counts* in subjects (n=40) receiving etrasimod without a titration scheme or placebo



**Only doses in ongoing clinical development presented*

Disclosures

Laurent Peyrin-Biroulet: honoraria from Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boehringer-Ingelheim, Lilly, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, and Samsung Bioepis; Ronald Christopher, Luba Trokan, Cheryl Lassen, and John Adams: employees of Arena Pharmaceuticals, Inc., San Diego, or its subsidiary; Tanja Kühbacher: consulting or lecturing fees from Abbvie, Ferring, Medtronic, Takeda, Falk, Janssen, MSD, Shire, Merckle Recordati, Mundipharma, and Celltrion.

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