AFFIDAVIT OF CHRISTOPHER BUTLER

1. I am the Office Manager at the Internet Archive, located in San Francisco, California. I make this declaration of my own personal knowledge.

2. The Internet Archive is a website that provides access to a digital library of Internet sites and other cultural artifacts in digital form. Like a paper library, we provide free access to researchers, historians, scholars, and the general public. The Internet Archive has partnered with and receives support from various institutions, including the Library of Congress.

3. The Internet Archive has created a service known as the Wayback Machine. The Wayback Machine makes it possible to surf more than 450 billion pages stored in the Internet Archive's web archive. Visitors to the Wayback Machine can search archives by URL (i.e., a website address). If archived records for a URL are available, the visitor will be presented with a list of available dates. The visitor may select one of those dates, and then begin surfing on an archived version of the Web. The links on the archived files, when served by the Wayback Machine, point to other archived files (whether HTML pages or images). If a visitor clicks on a link on an archived page, the Wayback Machine will serve the archived file with the closest available date to the page upon which the link appeared and was clicked.

4. The archived data made viewable and browseable by the Wayback Machine is compiled using software programs known as crawlers, which surf the Web and automatically store copies of web files, preserving these files as they exist at the point of time of capture.

5. The Internet Archive assigns a URL on its site to the archived files in the format http://web.archive.org/web/[Year in yyyy][Month in mm][Day in dd][Time code in hh:mm:ss]/[Archived URL]. Thus, the Internet Archive URL http://web.archive.org/web/19970126045828/http://www.archive.org/ would be the URL for the record of the Internet Archive home page HTML file (http://www.archive.org/) archived on January 26, 1997 at 4:58 a.m. and 28 seconds (1997/01/26 at 04:58:28). A web browser may be set such that a printout from it will display the URL of a web page in the printout's footer. The date assigned by the Internet Archive applies to the HTML file but not to image files linked therein. Thus images that appear on a page may not have been archived on the same date as the HTML file. Likewise, if a website is designed with "frames," the date assigned by the Internet Archive applies to the frameset as a whole, and not the individual pages within each frame.

6. Attached hereto as Exhibit A are true and accurate copies of printouts of the Internet Archive's records of the HTML files or PDF files for the URLs and the dates specified in the footer of the printout (HTML) or attached coversheet (PDF).

7. I declare under penalty of perjury that the foregoing is true and correct.

DATE: 7/2/18

Christopher Butler

Exhibit A

http://web.archive.org/web/20041021033354/http://www.fumapharm.ch:80/pdf
/BG-12_Schimrigk_Poster_Final.pdf

A PROSPECTIVE, OPEN-LABEL, PHASE II STUDY OF ORAL FUMARATE THERAPY FOR THE TREATMENT OF RELAPSING-REMITTING MULTIPLE SCLEROSIS

S. Schimrigk, N. Brune, K. Hellwig, M. Rieks, V. Hoffmann, D. Pöhlau, H. Przuntek, and the Fumarate Study Group for Multiple Sclerosis

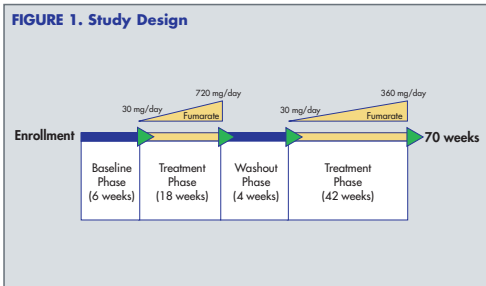Department of Neurology, St. Josef Hospital, Ruhr University Bochum, Bochum, Germany

642

INTRODUCTION

...osis (MS) is a chronic immune-mediated disease that results in ...demyelination and axonal loss in the central nervous system ...larly in the brain.

...evidence supports involvement of the immune system in the ...of MS[1]:

– ...e of lymphocytic infiltrates in CNS lesions and perivascular cuffing ...autoimmune response

...mune function in the pathology of MS is supported by the efficacy of ...dulating therapies in slowing disease progression

...chronic T-cell–mediated disease in which immune suppressants have ...nd to be effective and, similar to MS, a pro-inflammatory T-helper 1 ...profile predominates in lymphocytes isolated from psoriatic plaques.[2]

...and double-blind clinical studies have shown that oral fumarate therapy ...psoriasis.[3-7]

...olvement of immune-mediated responses and predominance of the ...profile in both psoriasis and MS, the objective of this study was to ...ral fumarate therapy is effective in patients suffering from relapsing-...(RRMS).

METHODS

...18 to 55 years of age and had a clinically definite diagnosis of RRMS ...e within the previous year.

...have had ≥1 active lesion on brain magnetic resonance imaging (MRI) ...Expanded Disability Status Scale (EDSS) score ≥2 but <6.

...eria for the study included

...ammatory diseases other than MS

...r breast feeding

...rug or alcohol abuse

...cerbation within the previous 3 weeks

...id treatment within the previous 30 days

...pressive therapy within the previous 12 weeks

...ign

...sign consisted of a 6-week baseline period and 2 treatment periods ...d 42 weeks) separated by a 4-week washout period without fumarate ...ure 1).

...marate was administered orally in tablet form as a low-dose (30 mg ...nitial®) and a high-dose (120 mg Fumaderm forte®) formulation

...marate was slowly increased over the first 9 weeks to minimize ...al side effects.

...dose of fumarate was 720 mg/day in the initial treatment phase and ...the second treatment phase.

...ination, EDSS score, ambulatory index (AI), and 9-Hole Peg Test (9-HPT) ...ed at screening, baseline visit, and weeks 3, 6, 12, 18, 22, 46, and 70.

• Brain MRI scans were performed at screening, baseline visit, and weeks 12, 18, 22, 46, and 70.

• Data were analyzed using the nonparametric Wilcoxon test. Differences were considered statistically significant at a P value of .05.

FIGURE 1. Study Design

Efficacy Outcomes

• The primary outcome measure was the number and volume of gadolinium-enhancing (Gd⁺) lesions on MRI scans.

• Secondary outcome measures were changes in EDSS score, AI, and 9-HPT.

RESULTS

• Demographic and baseline characteristics for patients enrolled in the study are presented in Table 1.

Table 1. Baseline Characteristics (N = 10)

Characteristic	Value
Sex, n (%)	
Female	5 (50)
Male	5 (50)
Median age, y (range)	29.5 (26–36)
Median relapse rate in preceding 12 months (range)	2 (1–3)
Median time since first event, y (range)	4.5 (1–11)
Median EDSS score (range)	2.0 (2.0–4.5)
Median AI	2.0
Median 9-HPT	
Right	22
Left	21

AI = ambulatory index; EDSS = Expanded Disability Status Scale; 9-HPT = 9-Hole Peg Test.

Table 2. Clinical Data

	Baseline	Week 12	Week 18	Week 22	Week 46	Week 70*
Median EDSS score	2.0	2.0	1.5	1.5	1.5	1.5
Median AI	2.0	2.0	1.0	1.0	1.0	1.0
Median 9-HPT (right), sec	22.0	20.0	20.5	17.0	18.0	19.0
Median 9-HPT (left), sec	21.0	20.5	20.5	18.0	19.0	19.0

*Calculated from 6 patients who completed the 70-week trial.
AI = ambulatory index; EDSS = Expanded Disability Status Scale; 9-HPT = 9-Hole Peg Test.

• 10 patients were enrolled, and 6 patients completed the 70-week study. Reasons for discontinuation were the following (one each):
  – Unplanned pregnancy
  – Side effects
  – Lack of compliance
  – Undetermined

• A significant reduction in the number of Gd⁺ lesions was observed following 18 weeks of oral fumarate treatment, with a further reduction after 70 weeks (Figure 2).

• The volume of Gd⁺ lesions was decreased at 22 weeks compared with baseline; this reduction was maintained at 46 and 70 weeks (Figure 3).

• Patients who completed the study demonstrated stable or slightly improved clinical measures of disease, including EDSS score, AI, and 9-HPT over the course of the study (Table 2), although the changes did not achieve statistical significance.

• Mild to moderate gastrointestinal side effects were experienced by 6 of 7 patients who completed >3 weeks of treatment but decreased during the first 12 weeks of treatment. In 1 patient these side effects were severe enough to discontinue treatment.

• Other side effects were mild and transient. Four patients had a transient increase in liver enzymes.

FIGURE 2. Change in Number of Gadolinium-Enhancing Lesions
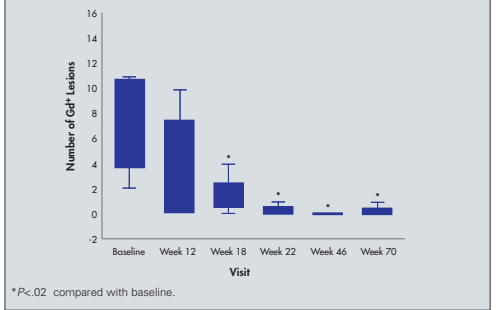
*P<.02 compared with baseline.

FIGURE 3. Change in Volume of Gadolinium-Enhancing Lesions
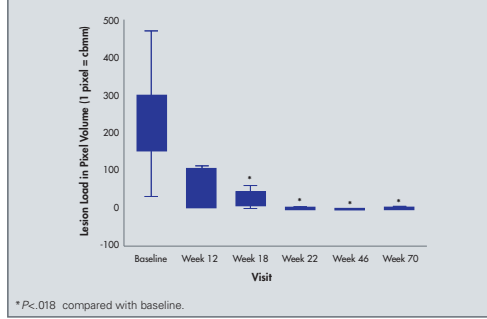
*P<.018 compared with baseline.

CONCLUSIONS

• Oral fumarate therapy resulted in a significant improvement in the number and volume of Gd⁺ lesions compared with baseline.

• Clinical measures of both function and disease progression appeared stable during the study, supporting the MRI results.

• The positive results in this small, short-term study suggest that larger trials should be undertaken to determine the efficacy of oral fumarate therapy in patients with MS.

References
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- Multiple sclerosis (MS) is a chronic immune-mediated disease that results in focal areas of demyelination and axonal loss in the central nervous system (CNS), particularly in the brain.

- Considerable evidence supports involvement of the immune system in the pathogenesis of MS[1]:
  - The presence of lymphocytic infiltrates in CNS lesions and perivascular cuffing suggests an autoimmune response
  - A role for immune function in the pathology of MS is supported by the efficacy of immune-modulating therapies in slowing disease progression

- Psoriasis is a chronic T-cell–mediated disease in which immune suppressants have also been found to be effective and, similar to MS, a pro-inflammatory T-helper 1 (Th1) cytokine profile predominates in lymphocytes isolated from psoriatic plaques.[2]

- Several open and double-blind clinical studies have shown that oral fumarate therapy is effective in psoriasis.[3-7]

- Given the involvement of immune-mediated responses and predominance of the Th1 cytokine profile in both psoriasis and MS, the objective of this study was to determine if oral fumarate therapy is effective in patients suffering from relapsing-remitting MS (RRMS).
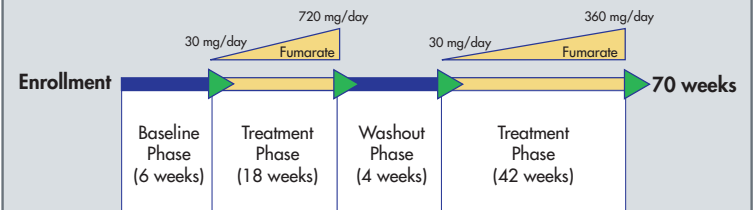
METHODS

Patients

- Patients were 18 to 55 years of age and had a clinically definite diagnosis of RRMS with ≥1 relapse within the previous year.

- Patients must have had ≥1 active lesion on brain magnetic resonance imaging (MRI) and a baseline Expanded Disability Status Scale (EDSS) score ≥2 but <6.

- Exclusion criteria for the study included
  - Infection
  - Chronic inflammatory diseases other than MS
  - Pregnancy or breast feeding
  - History of drug or alcohol abuse
  - Disease exacerbation within the previous 3 weeks
  - Corticosteroid treatment within the previous 30 days
  - Immunosuppressive therapy within the previous 12 weeks

Study Design

- The study design consisted of a 6-week baseline period and 2 treatment periods (18 weeks and 42 weeks) separated by a 4-week washout period without fumarate treatment (Figure 1).
  - Dimethylfumarate was administered orally in tablet form as a low-dose (30 mg Fumaderm initial®) and a high-dose (120 mg Fumaderm forte®) formulation

- The dose of fumarate was slowly increased over the first 9 weeks to minimize gastrointestinal side effects.

- The maximum dose of fumarate was 720 mg/day in the initial treatment phase and 360 mg/day in the second treatment phase.

- Physical examination, EDSS score, ambulatory index (AI), and 9-Hole Peg Test (9-HPT) were performed at screening, baseline visit, and weeks 3, 6, 12, 18, 22, 46, and 70.

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AI = ambulatory index; EDSS = Expanded Disability Status Scale; 9-HPT = 9-Hole Peg Test.

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