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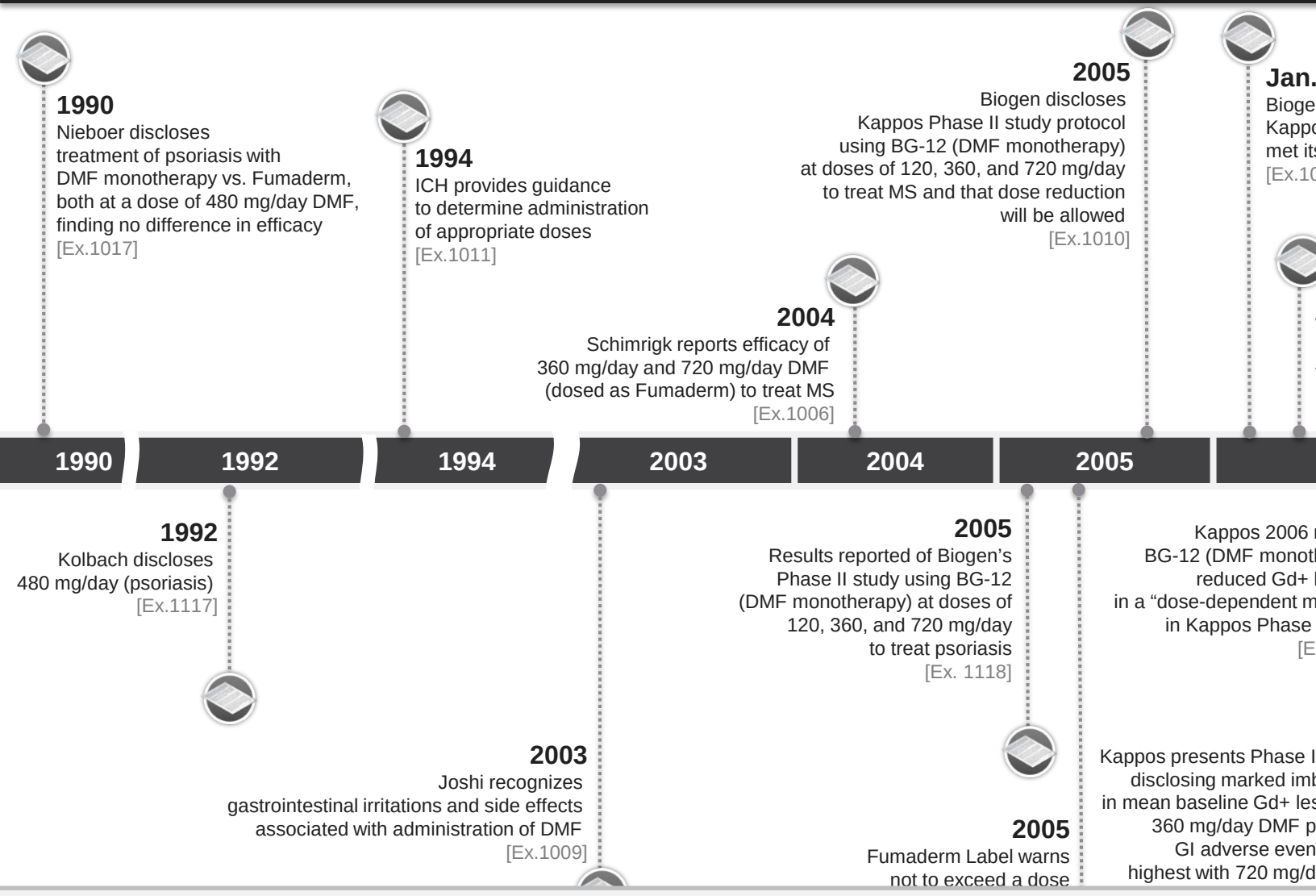
MYLAN PHARMACEUTICAL
SAWAI USA, INC
SAWAI PHARMACEUTICAL CO
Peti

BIOGEN MA
Patent

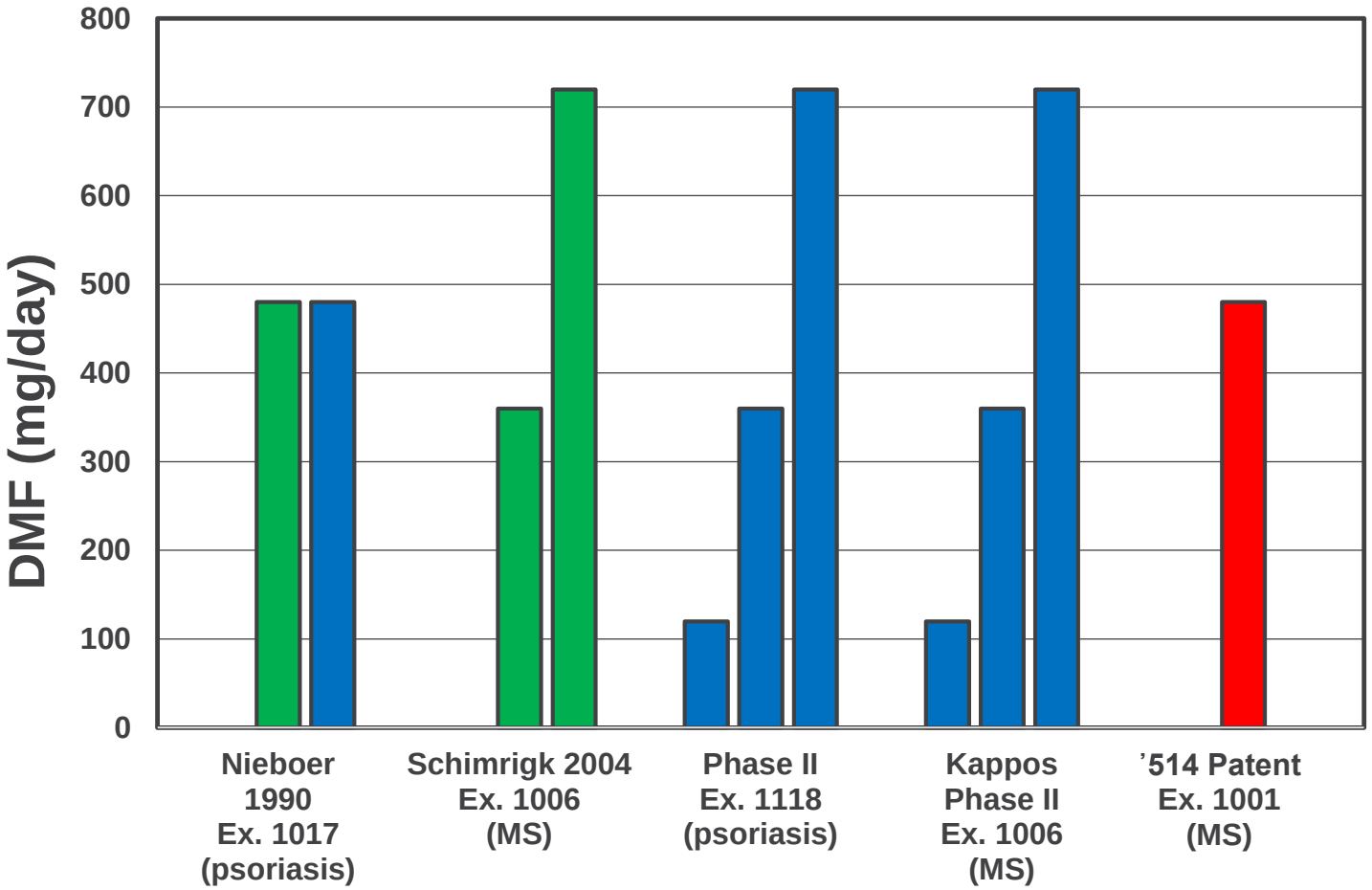
Mylan

Case IPR201
Patent No. 8

Prior Art Timeline



DMF Dosing Disclosed in the Prior A



Prior Art Points to 480 mg/day DMF Dosing to Tr

Prior Art	Regimen	Conclusion
Nieboer 1990 (Ex.1017)	**480 mg/day DMF vs. 480 mg/day DMF (Fumaderm)**	• Discloses that there is no difference between treatment Fumaderm at a dose of 480 mg/day DMF in patients wit 2, 6.
Kolbach 1992 (Ex.1117)	**240 mg/day DMF vs. 480 mg/day DMF (Fumaderm)**	• "Apparently a dosage of 480 mg of DMFAE per day is n achieve a satisfactory improvement in approximately 50 patients." *Id.* at 2.
Drugs 2005 (Ex.1118)	**120, 360, 720 mg/day DMF (BG-12)**	• Dose ranging study of 120, 360, 720 mg/day DMF to tre 6-7.
Schimrigk 2004 Abstract (Ex.1006)	**360 mg/day and 720 mg/day DMF (Fumaderm)**	• Suggests range of 360 mg/day to 720 mg/day doses of in treating MS. *Id.* at 5.
Clinical Trials (Ex.1010)	**120, 360, 720 mg/day DMF (BG-12)**	• "Dose reduction will be allowed for subjects who are una investigational drug." *Id.* at 2.
January 2006 Press Release (Ex.1005)	**120, 360, 720 mg/day DMF (BG-12)**	• "Phase II study designed to evaluate the efficacy and sa oral fumarate, in patients with relapsing-remitting multip met its primary endpoint." *Id.* at 1.
Kappos 2006 (Ex.1007)	**120, 360, 720 mg/day DMF (BG-12)**	• "BG00012 significantly reduces brain lesion activity, in a manner, as measured by MRI in patients with RRMS." *I*
Kappos 2006 Presentation (Ex.1046)	**120, 360, 720 mg/day DMF (BG-12)**	• Discloses an over three-fold difference in mean baseline 360 mg/day DMF group v. placebo. *Id.* at 17. • 720 mg/day dose produced highest number of GI seriou and adverse events, and highest discontinuation rate. *Id*
WO '342		• Discloses 480 mg/day DMF to treat autoimmune diseas

Administration of 480 mg/day DMF to Treat M
Was Obvious

The Problem	• Fumarates such as DMF were known to cause side effects such as gastrointestinal p flushing
The Motivation	• GI and flushing side effects seen with 720 mg/day DMF (dosed as Fumaderm or BG- • Patients prefer less frequent dosing • 480 mg/day DMF within the range of efficacious DMF doses to treat MS (360 and 72 • Prior art taught dose of 480 mg/day DMF to treat psoriasis, an autoimmune disease w immunopathologic pathway similar to MS
The Solution	• Follow prior art to less frequent 480 mg/day BID dosing while reducing side effects ar compliance to optimize the dose
Prior Art	• 480 mg/day DMF in immunologically similar disease psoriasis [Exs. 1017] • 360 mg/day and 720 mg/day DMF (Fumaderm) in MS [Ex. 1006] • 120, 360, 720 mg/day DMF (BG-12) in psoriasis and MS [Exs. 1118, 1007]
The Grounds	• January 2006 Press Release [Ex. 1005] + Schimrigk 2004 Abstract [Ex. 1006] • Kappos 2006 [Ex. 1007] + Schimrigk 2004 Abstract [Ex. 1006] • Kappos 2006 [Ex. 1007] + WO '342 [Ex. 1008] • Kappos 2006 [Ex. 1007], Clinical Trials [Ex. 1010], Joshi '999 [Ex. 1009], ICH Guidelines [E
Alleged Secondary Considerations	• Magnitude of effect from 480 mg/day DMF dose in DEFINE/CONFIRM trials was not • No nexus for commercial success due to disincentives from Biogen's existing and po rights and extensive marketing for Tecfidera • Any commercial success was fueled by factors beyond the claims of the '514 patent

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