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| <b>Name of company:</b><br>Duramed Research, Inc.,<br>Subsidiary of Barr<br>Pharmaceuticals, Inc.  | <b>Trial Synopsis</b>                                    | <br>© Duramed Research, Inc.<br>Subsidiary of Barr Pharmaceuticals, Inc.<br>This Tabulated Study Report is property of Duramed<br>Research, Inc. and may not – full or in part – be<br>passed on, reproduced, published or otherwise used<br>without the express permission of Duramed<br>Research, Inc. |
| <b>Name of finished product:</b><br>Seasonale®   |  |  |
| <b>Name of active ingredient:</b><br>Seasonale®: levonorgestrel 150 µg; ethinyl estradiol 30µg x 84 days, placebo x 7 days   |  |  |
| <b>Trial Number:</b><br>SEA-301A   | <b>Study period (dates):</b><br>9 DEC 2001 – 19 MAY 2004 |  |
| <b>Title of Study:</b><br>A Phase IIIb, Parallel, Multicenter, Open-Label Clinical Study To Evaluate The Safety Of Seasonale®<br>Extended Oral Contraceptive Therapy – 84-Day Active Cycle   |  |  |
| <b>Investigator:</b> Multiple investigators  |  |  |
| <b>Study centers:</b> 27 Centers – all in the U.S.   |  |  |
| <b>Publication (Reference):</b> Anderson FD, Gibbons W, Portman D. Long-term safety of an extended-cycle oral<br>contraceptive (Seasonale®): a 2-year multicenter open-label extension trial. American Journal of Obstetrics &<br>Gynecology. Jul 2006;195(1):92-96.   |  |  |
| <b>Link to Labeling:</b> <a href="http://www.seasonale.com/pdf/Seasonale_prescribing_info.pdf">http://www.seasonale.com/pdf/Seasonale_prescribing_info.pdf</a>   |  |  |
| <b>Clinical phase:</b> Phase IIIb  |  |  |
| <b>Objectives:</b> The primary objective was to demonstrate the safety of the Seasonale® extended-cycle for up to<br>an additional 2 years in women who had participated in the Phase 3 Seasonale clinical trial (SEA – 301).  |  |  |
| <b>Methodology:</b> Open-label, non-randomized multicenter study of Seasonale® in patients who successfully<br>completed one year of therapy in study SEA-301. Patients who received either 28-day Nordette®, Duramed<br>Pharmaceuticals, Inc) or 91-day (Seasonale®) OC treatments in the earlier study were assigned to the 91-day<br>Seasonale regimen.   |  |  |
| <b>Numbers of patients:</b><br>Seasonale®: N= 189 treated<br>LNG 100 µg; EE µg 20µg: N= 161 treated  |  |  |
| <b>Diagnosis and Main Criteria for Inclusion:</b> Patients were sexually active adult females of child bearing<br>potential, in a heterosexual relationship, at risk for pregnancy, fluent in English, who were in good health and<br>who successfully completed one year of therapy while enrolled in study SEA-301. Patients must have had a<br>negative urine pregnancy test before enrollment and agreed to use study oral contraceptive therapy as their<br>primary birth control method. |  |  |
| <b>Test Product Dose, Duration, and Route of Administration:</b><br>Seasonale®: levonorgestrel (150 µg); ethinyl estradiol (30µg) administered orally for four 91-day cycles (84<br>days active drug; 7 days placebo)<br>LNG 100 µg; EE µg 20µg: levonorgestrel (LNG) 100 µg; ethinyl estradiol (EE) 20 µg administered orally for<br>four 91-day cycles (84 days active drug; 7 days placebo)   |  |  |
| <b>Reference Product Dose, Duration, and Route of Administration:</b><br>No reference products were used in this study   |  |  |
| <b>Criteria for Evaluation:</b><br><b>Efficacy:</b> Prevention of pregnancy<br><b>Safety:</b> Adverse events, clinical laboratory evaluation (blood chemistry, hematology, urinalysis), vital signs,<br>physical examination, bleeding and spotting.   |  |  |
| <b>Statistical Methods:</b><br><b>Efficacy:</b> Crude pregnancy rate. No comparative statistical tests were conducted.<br><b>Safety:</b> Descriptive statistics.   |  |  |

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| <b>Summary:</b><br>In addition to the safety results reported for Seasonale®, a separate cohort looked at a lower dosage extended cycle regimen with LNG/EE 100mcg/20mcg. This report represents results for Seasonale®<br><br>As this was primarily a long-term safety study of Seasonale®, no formal efficacy evaluation was planned other than a simple calculation of the proportion of treated patients who became pregnant.<br><br><u>Efficacy Results:</u> Three patients who were noncompliant with study medication became pregnant while on Seasonale®. Seven patients became pregnant after stopping Seasonale®, all within 6 months following their last dose (5 of these patients discontinued from the study because of a desire to become pregnant) One participant desiring pregnancy became pregnant around the time she discontinued from the study.   |  |  |
| <u>Safety Results:</u> Serious adverse events were reported in 5 patients during this 2-year extension study, 1 report each of vulva cancer, bile duct stone, major depressive disorder, cholecystitis, and uterine fibroids. Only the reports of cholecystitis (possibly related) and bile duct stone (remotely related) were considered by the investigator to have any relationship to the study medication.<br><br>Adverse events leading to discontinuation included: some aspect of bleeding and/or spotting (n=7) [though not necessarily unscheduled bleeding and/or spotting], uterine fibroids (n=2) and cholelithiasis (n=1) Overall rates of study discontinuation and the incidence of adverse events (including serious adverse events and adverse events leading to study discontinuation) were consistent with those reported in study SEA-301.<br><br>The most frequently reported adverse events were sinusitis (19.1%), headache (16.9%), nasopharyngitis (16.4%), upper respiratory tract infection (16.4%), urinary tract infection (10.1%), and dysmenorrhea (9.5%)<br><br><u>Cycle Control:</u> The observed number of patient electronic diary-reported total days, unscheduled days, and scheduled (withdrawal) days of bleeding and/or spotting and bleeding alone were lower than those observed in the one-year study SEA-301. |  |  |