Evidence Table 7. Trials of dual therapy with pegylated interferon plus ribavirin: dose effects

| **Author, Year Country Study Name Quality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **Age Sex Race** | **Genotype Severity of Liver Disease Proportion Treatment-Naïve** |
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| Abergel, 200647 France  Pegylated interferon alpha-2b plus ribavirin for treatment of chronic hepatitis C with severe fibrosis: a multicenter randomized controlled trial comparing two doses of Pegylated interferon alpha-2b  Overall Quality: Fair | A: (standard-dose) Pegylated interferon alpha-2b 1.5 µg/kg 1x/week/48 weeks B: (low-dose) Pegylated interferon alpha-2b 0.75 µg/kg 1x/week/48 weeks | A: Ribavirin  800 mg/day/48weeks B: Ribavirin  800 mg/day/48 weeks | None | Age between 18 and 75 years No previous treatment with IFN and/or ribavirin Alanine aminotransferase (ALT) > upper limit of normal (ULN) at least once during the last 12 months Positive serum HCV-RNA using qualitative polymerase chain reaction (PCR) and severe fibrosis on liver biopsy defined by a METAVIR fibrosis stage of F3 or F4 at histological examination of the liver | Recent history of alcohol abuse or IV drug addiction Hemoglobin <12 g/dL in women and <13 g/dL in men Platelets <75 000/lL Neutrophils <1500/lL Decompensated cirrhosis (ascites, variceal hemorrhage encephalopathy) Albumin <30 g/L Prothrombin <60% Bilirubin >34 lmol/L HCC Chronic hepatitis B infection HIV infection | NR/210/ 210/203 | A vs. B Age(Mean): 49.3 vs. 51.1 years   Female: 36% vs. 32%  Race: NR | A vs. B Genotype 1 - 50/101(49.5%) vs. 54/102(529%) Genotype 2 - 11/101(10.9%) vs. 9/102(8.8%) Genotype 3 - 30/101(29.7%) vs. 28/102(27.5%)  Genotype 4 - 5/101(5%) vs. 4/102(3.9%) Genotype 5 - 5/101(5%) vs. 7/102(6.9%)  Fibrosis stage:  F3 - 55/101(54.4%) vs. 44/102(43.1%) F4 - 46/101(45.6%) vs. 58/102(56.9%)  Cirrhosis: 46% vs. 57%  100% Treatment naïve |

| **Author, Year Country Study Name Quality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Abergel, 200647 France  Continued | Followup visits at 24 weeks after completion of treatment | A vs. B ETR: 59/101(62.8%) vs. 57/102(59.4%)  SVR: 50/101(49.5%) vs. 38/102(37.2%) | A vs. B ETR: NR  SVR:  BMI <27 kg/m2 - 35/70 (50.0%) vs. 26/70 (37.1%); p=NS BMI >27 kg/m2 - 10/31 (32.3%) vs. 12/32 (37.5%); p=NS  gamma glutamyl transpeptidase (GGT) used as a marker for steatosis: GGT <1.6 ULN - 29/48 (60.4%) vs. 23/48 (47.9%); p=NS GGT >1.6 ULN - 13/50 (26.0%) vs. 13/51 (25.5%); p=NS | A vs. B ETR: NR  SVR:  Genotypes 1, 4, 5, - 15/60(25.0%) vs. 11/65 (16.9%); p=NS Genotype 1 - 12/50 (24.0%) vs. 09/54 (16.7%); p=NS Genotypes 2, 3 - 30/41 (73.2%) vs. 27/37 (73.0%); p=NS  Viremia <800.000 IU/mL - 25/55 (45.5%) vs. 20/47 (42.5%); p=NS Viremia >800 000 IU/mL - 20/44 (45.5%) vs. 17/53 (32.1%); p=NS  Cirrhosis (F4) - 18/46 (39.1%) vs. 20/58 (34.5%); p=NS Severe fibrosis(F3) - 27/55 (49.1%) vs. 18/44 (40.1%); p=NS | None | A vs. B Discontinuation - 30/101(31 %) vs. 28/102(27 %) Discontinuation or treatment reduction – 53/101(54%) vs. 37/102(36 %), p <0.03 Treatment reduction - 36/101(37%) vs. 13/102(12%), p <0.0002 Overall withdrawals - NR Deaths - NR  Severe Adverse Events:  Adverse event - 8/101(9%) vs. 4/102(3%) Cytopenia -7/101(7%) vs. 1/102(1%) Others - 7/101(8%) vs. 3/102(2 %)  Adverse events Adverse event - 15/101(16%) vs. 4/102(3%), p <0.01 Cytopenia - 20/101(21 %) vs. 9/102(8%), <0.03 Anemia - 9/101(10%) vs. 5/102(4 %) Neutropenia - 10/101(11 %) vs. 4/102(3%) Thrombopenia - 3/101(3 %) vs. 0/102(0%) Others - 2/101(1%) vs. 0/102(1%) Hemoglobin < 10g/dL - 27/101(27 %) vs. 16/102(15%), p=0.054 Neutrophils < 750/ µL - 21/101(21%) vs. 8/102(7%), p <0.01 Platelets < 50 000/ µL - 7/101(7%) vs. 7/102(6 %) Depression - 13/101(12%) vs. 15/102(14%) Suicide - 2/101(1%) vs. 0/102(0%) Hypothyroidism (treated) - 9/101(10%) vs. 1/102(.5%) | Schering-Plough, France and Delegation Regionale a la Recherche Clinique, Clermont-Ferrand, France |

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| **Author, Year Country Study Name Quality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **Age Sex Race** | **Genotype Severity of Liver Disease Proportion Treatment-Naïve** |
| Brady, 201048 United States  Induction pegylated interferon alfa-2b combination with ribavirin in patients with genotype 1 and 4 chronic hepatitis C: a prospective, randomized, multicenter, open-label study  Overall Quality: Fair | A. Pegylated interferon alfa-2b 3.0 mcg/kg/week for 12 weeks followed by 1.5 mcg/kg/week for 36 weeks B. Pegylated interferon alfa-2b 1.5 mcg/kg/week for 48 weeks | A. 800-1400 mg/day for 48 weeks B. 800-1400 mg/day for 48 weeks | NA | Treatment-naïve patients Genotype 1 or 4 Positive HCV antibodies and detectable HCV RNA Liver biopsy consistent with viral hepatitis within the past 48 months Cirrhosis no worse than Child-Pugh Class A Hemoglobin >12 g/dL in females and 13 g/dL in males White blood cells >3000 Neutrophil >1500 Platelet > 65K Direct bilirubin within 20% of upper limits of normal Creatinine within 20% of upper limits of normal Albumin within normal limits | Non genotype 1 or 4 HCV infection Decompensated liver disease Evidence of coexisting liver disease Coinfection with HIV or HBV Hemochromatosis Alpha-1 antitrypsin deficiency Wilson disease Autoimmune hepatitis Alcoholic liver disease Hepatocellular carcinoma Pregnancy Psychiatric conditions Significant cardiovascular dysfunction within the past 1 year Poorly controlled diabetes mellitus Chronic pulmonary disease Clinically significant retinal abnormalities Immunologically mediated diseases Any medical condition requiring systemic steroids Active clinical gout Substance abuse in the past 6 months | NR/NR/ 623/610 | A vs. B Age mean: 45 vs. 45 Female: 50% vs. 50% non White: 32% vs. 28% | A vs. B genotype 1: 99% vs. 99% Treatment-naïve: all Fibrosis stage 3 or 4: 26% vs. 23% HCV- RNA >800K: 71% vs. 62% |

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| **Author, Year Country Study Name Quality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
| Brady, 201048 United States  Continued | 24 weeks following treatment completion | A vs. B ETR: 126/299 (42.1%) vs. 121/311 (38.9%); p=  SVR: 96/299 (32.1%) vs. 92/311 (29.6%); p=0.434 | A vs. B Black: 13/36 (36.1%) vs. 12/37 (32.4%); p=0.9 Hispanic: 29.9% vs. 22.5%; p=0.292 (absolute numbers NR)  Weight <85 kg: 26% vs. 31% (p=NS); (absolute numbers NR) Weight >85 kg: 38% vs. 28% (p=0.08); (absolute numbers NR) | NR | NR | A vs. B Overall withdrawals: 146/299 (48.8%) vs. 133/311 (42.7%); p=0.2 Withdrawals for adverse events: NR Serious adverse events: NR Deaths: NR  Neutropenia <500: 10/299 (3.4%) vs. 5/311 (1.6%); p=0.261 Anemia hemoglobin <10: 50/299 (16.7%) vs. 50/311 (16.1%); p=0.916 Thrombocytopenia platelets <50: 3/299 (1.0%) vs. 4/311 (1.3%); p=1.0 Pyrexia: 68/299 (22.7%) vs. 80/311 (25.7); p=0.445 Myalgia: 114/299 (38.1%) vs. 108/311 (34.7%); p=0.430 Rash: 34/299 (11.4%) vs. 58/311 (18.6%); p=0.016 Fatigue: 131/299 (43.8%) vs. 156/311 (50.2%); p=0.136 Headache: 30/299 (10.0%) vs. 47/311 (15.1%); p=0.077 Insomnia: 47/299 (15.7%) vs. 51/311 (16.4%); p=0.906 Depression: 55/299 (18.4%) vs. 70/311 (22.5%); p=0.247 Nausea: 37/299 (12.4%) vs. 40/311 (12.9%); p=0.953 | Schering Plough |

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| **Author, Year Country Study Name Quality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **Age Sex Race** | **Genotype Severity of Liver Disease Proportion Treatment-Naïve** |
| Bronowicki, 200646 France  Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirin  Overall Quality: Fair | A. Pegylated interferon alfa-2a 180 mcg/week for 48 weeks B. Pegylated interferon alfa-2a 180 mcg/week for 48 weeks | All patients treated for 24 weeks of ribavirin 400 mg twice daily. At week 24 patients with indictable HCV RNA were randomized at week 26 to 22 more weeks (48 weeks total) of: A. 400 mg twice daily B. Placebo | NA | Treatment naïve Aged >18 years HCV genotype 1 infection HCV RNA >600 IU/mL Increased ALT levels documented 2 times in last 6 months Liver biopsy consistent with chronic hepatitis C obtained within 18 months before therapy | chronic liver disease of other etiology Evidence of decompensation Coinfection with HBV or HIV Neutrophils <1500/mm3 platelets <90,000/mm3 Hemoglobin level less than 12 g/dL (women) or less than 13 g/dL (men) Risk factor for anemia Serum creatinine >1.5 times upper limit of number Severe psychiatric disease Significant comorbid medical conditions | NR/516/ 349/349 | A vs. B Age mean: 44.2 vs. 45.4 Female: 43% vs. 43% Non White: NR | A vs. B Genotype 1: all HCV RNA>800,000: 62% vs. 71% Fibrosis score F3 or F4: 27% vs. 28% |

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| **Author, Year Country Study Name Quality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
| Bronowicki, 200646 France  Continued | 24 weeks following treatment completion | A vs. B SVR: 93/176 (52.8%) vs. 118/173 (68.2%); p=0.004  Hepatitis Quality of Life Questionnaire: Scores for all domains not significantly different between two treatment regimens at any point in time | NR | NR | NR | A vs. B Overall withdrawals: NR Withdrawals for adverse events: 3/173 (1.7%) vs. 4/176 (2.3%); p=NS Serious adverse events: 13/173 (7.5%) vs. 12/176 (6.8%); p=NS Deaths: 1/173 (0.5%) vs. 0/176 (0%); p=NS Asthenia: 19/173 (10.6%) vs. 13/176 (7.3%); p=NS Headache: 7/173 (3.9% ) vs. 6/176 (3.4%); p=NS Depression: 13/173 (7.5%) vs. 16/176 (9.1%); p=NS Myalgia: 6/173 (3.4%) vs. 6/176 (3.4%); p=NS Leukopenia: 5/173 (2.8%) vs. 5/176 (2.8%); p=NS | Roche |

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| **Author, Year Country Study Name Quality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **Age Sex Race** | **Genotype Severity of Liver Disease Proportion Treatment-Naïve** |
| Ferenci, 200849 Austria  A Randomized, Prospective Trial of Ribavirin 400 mg/Day Vs. 800 mg/Day in Combination with Pegylated interferon Alfa-2a in Hepatitis C Virus Genotypes 2 and 3  Overall Quality: Fair | A: Pegylated interferon alpha-2a 180 μg/week/24 weeks B: Pegylated interferon alpha-2a 180 μg/week/24 weeks | A: Ribavirin  800 mg/day/24 weeks B: Ribavirin  400 mg/day/24 weeks | None | Treatment-naive adult Aged 18 to 65 years Chronic hepatitis C HCV genotype 2 or 3 infection Quantifiable HCV RNA in serum and elevated serum ALT activity (1.5 times the upper limit of normal [ULN] in the previous 6 months and during screening)  Hemoglobin value 12 g/dL (women) or 13 g/dL (men)  Leukocyte count 3000/ L Platelet count 100,000/ L Serum creatinine level 1.5 times the ULN. Women of childbearing potential were required to have a negative pregnancy test within 24 hours of the first dose All fertile male and female participants were required to use two forms of effective contraception during treatment and for 6 months after the end of treatment | Pregnant or breast-feeding women and male partners of pregnant women  Received prior treatment with interferon or ribavirin at any time Co infected with hepatitis B virus or human immunodeficiency virus Decompensated liver disease or chronic liver disease attributable to another cause Coronary heart disease Diabetes mellitus requiring insulin therapy Autoimmune disorders Any other unstable chronic medical condition Severe psychiatric disease, especially depression History of active alcohol or drug addiction within the previous 6 months  \*Patients on opiate substitution therapy were eligible if they were treated by the drug treatment centre in the Department of Psychiatry, Medical University of Vienna | 291/282/ 250/250 | A vs. B Age (Mean): 37 vs. 36 years   Female: 40% vs. 38%  Race: NR | A vs. B Genotype 2 – 18/141(13%) vs. 19/141(14%) Genotype 3 - 123/141(87%) vs. 122/141(86%)  Severity of liver disease- HCV RNA < 800,000 IU/mL - 5.9 vs. 5.7  Cirrhosis: NR  Minimal or no fibrosis: NR 100% Treatment naïve |

| **Author, Year Country Study Name Quality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Ferenci, 200849 Austria  Continued | Followup visits at 24 weeks after completion of treatment | A vs. B ETR: NR  SVR: 97/141(68.8%) vs. 90/141(63.8%) | NR | A vs. B SVR: Genotype 2 - 14/18(77.8%) vs. 12/16(63.2%); p=NS Genotype 3 - 83/12(67.5%) vs. 78/122(63.9%); p=NS | NR | A vs. B Overall withdrawals: 13/141 (9%) vs. 22/141 (16%) p=NS Withdrawals due to adverse events: NR Deaths: NR Severe Adverse Events: NR  Adverse events:  Pruritus: 48/141 (34%) vs. 50/141 (35%); p=NS Psychiatric events (mostly depression): 49/141 (35%) vs. 56/141 (40%); p=NS Hemoglobin <8.5 g/dL: 2/141 (1.4%) vs. 1/141 (0.7%); p=NS Neutrophils <1000/mm3: 73/141 (52%) vs. 71/141 (50%); p=NS Platelets <50K/mm3: 6/141(4%) vs. 6/141 (4%); p=NS | Roche, Austria |

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| **Author, Year Country Study Name Quality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **Age Sex Race** | **Genotype Severity of Liver Disease Proportion Treatment-Naïve** |
| Fried., 200850 USA  Improved Outcomes in Patients with Hepatitis C with Difficult-to-Treat Characteristics: Randomized Study of Higher Doses of Pegylated interferon ά-2a and Ribavirin  Overall Quality: Fair | A: Pegylated interferon alfa-2a 180 μg/week/48 weeks  B: Pegylated interferon alfa-2a 180 μg/week/48 weeks C: Pegylated interferon alfa-2a 270 μg/week/48 weeks D: Pegylated interferon alfa-2a 270 μg/week/48 weeks | A: Ribavirin 1200 mg/day/48 weeks B: Ribavirin 1600 mg/day/48 weeks C: Ribavirin 1200 mg/day/48 weeks D: Ribavirin 1600 mg/day/48 weeks | None | Treatment-naïve Age 18 years or older Weighing 85 kg  Chronic hepatitis C infection with genotype 1  Baseline HCV RNA level 800,000 IU/mL determined by quantitative polymerase chain reaction (PCR) assay Positive anti-HCV antibody test Elevated serum alanine aminotransferase level within the previous 6 months Compensated liver disease Liver biopsy specimen consistent with chronic hepatitis C obtained within the previous 24 months | Infection with an HCV genotype other than 1 Previous treatment with interferon-based therapy, ribavirin, or any investigational drug for chronic hepatitis C History or other evidence of liver disease not associated with chronic hepatitis C Neutrophil count 1.5 x 10^9 cells/L Platelet count 90  109 cells/L Hemoglobin level 12 g/dL in women and 13 g/dL in men  Increased risk of anemia or for whom anemia would be medically problematic Serum creatinine level more than 1.5 times the upper limit of normal Co infection with hepatitis B virus or human immunodeficiency virus Other serious chronic disease History of severe psychiatric disease (a history of a suicide attempt, hospitalization or period of disability due to psychiatric disease, and/or a Beck Depression Inventory score 20) Evidence of alcohol or drug abuse within 1 year of study entry | 301/193/ 188/187 | A vs. B vs. C vs. D Age (Mean): 47.1 vs. 49.6 vs. 47.1 vs. 48.5 years  Female: 20% vs. 13% vs. 26% vs. 21%  Race:  White - 70% vs. 62% vs. 74% vs. 68% Non White- 30% vs. 38% vs. 26% vs. 32% | A vs. B vs. C vs. D Genotype 1 – 100%  Histologic diagnosis: Non cirrhotic -83% vs. 81% vs. 83% vs. 81% Cirrhosis - 17% vs. 19% vs. 17% vs. 19%  HCV RNA (IU/mLx106): 4.9 vs. 6.2 vs. 5.5 vs. 5.2  100% Treatment naïve |

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| **Author, Year Country Study Name Quality** | | | **Duration of Followup** | **Outcome** | | | **Subgroup Analyses** | | **Subgroup Analyses** | | **Histologic Response** | **Adverse Events** | | | | **Funding Source** | |
| Fried, 200850 USA  Continued | | | Followup visits at 24 weeks after completion of treatment | A vs. B vs. C vs. D ETR: 21/46(45.7%) vs. 27/47(57.4%) vs. 26/47(55.3%) vs. 26/47(55.3%)  SVR: 13/46(28.3%) vs. 15/47(31.9%) vs. 17/47(36.2%) vs. 22/47(46.8%) | | | NR | | NR | | NR | A vs. B vs. C vs. D Overall withdrawals: 13/46(28%) vs. 9/47(19%) vs. 15/47(32%) vs. 17/47(36%) Withdrawals for adverse events: 5/46(11%) vs. 1/47(2%) vs. 7/47(15%) vs. 9/47(19%) Deaths: NR Serious Adverse Events: 4/46(9%) vs. 6/47(13%) vs. 6/47(13%) vs. 5/47(11%)  Adverse events: (significant p-values noted for A vs. B, A vs. C, or C vs. D)  Fatigue - 36/46(78%) vs. 32/47(68%) vs. 35/47(74%) vs. 34/47(72%) Headache - 24/46(52%) vs. 18/47(38%) vs. 22/47(47%) vs. 21/47(45%)  Insomnia - 18/46(39%) vs. 20/47(43%) vs. 22/47(47%) vs. 24/47(51%) Nausea - 18/46(39%) vs. 20/47(43%) vs. 18/47(38%) vs. 18/47(38%)  Chills - 15/46(33%) vs. 14/47(30%) vs. 19/47(40%) vs. 17/47(36%)  Myalgia - 14/46(30%) vs. 16/47(34%) vs. 19/47(40%) vs. 16/47(34%)  Depression - 14/46 (30%) vs. 20/47(43%) vs. 12/47(26%) vs. 16/47(34%)  Arthralgia - 13/46(28%) vs. 16/47(34%) vs. 16/47(34%) vs. 15/47(32%)  Irritability - 14/46(30%) vs. 14/47(30%) vs. 12/47(26%) vs. 16/47(34%)  Pyrexia - 12/46(26%) vs. 14/47(30%) vs. 16/47(34%) vs. 14/47(30%)  Rash - 12/46(26%) vs. 11/47(23%) vs. 15/47(32%) vs. 12/47(26%)  Diarrhea - 12/46(26%) vs. 9/47(19%) vs. 11/47(23%) vs. 10/47(21%)  Cough - 9/46(20%) vs. 12/47(26%) vs. 12/47(26%) vs. 8/47(17%) Dyspnea - 9/46(20%) vs. 12/47(26%) vs. 8/47(17%) vs. 12/47(26%)  Dizziness - 12/46(26%) vs. 9/47(19%) vs. 7/47(15%) vs. 9/47(19%)  Back pain - 1/46(2%) vs. 11/47(23%) vs. 4/47(9%) vs. 3/47(6%); (B vs. D p=0.02) Injection site erythema - 10/46(22%) vs. 9/47(19%) vs. 6/47(13%) vs. 5/47(11%) | | | | Hoffman La Roche | |
| **Author, Year Country Study Name Quality** | **Interferon Regimen** | | | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | | **Eligibility** | | **Exclusion** | | | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **Age Sex Race** | **Genotype Severity of Liver Disease Proportion Treatment-Naïve** | |
| Helbling, 200651 Switzerland  HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon α-2a and ribavirin  Overall Quality: Fair | A: Pegylated interferon alpha-2a 180 μg/week/48 weeks B: Pegylated interferon alpha-2a 180 μg/week/48 weeks | | | A: (standard dose)Ribavirin  <75 kg - 1000 mg/day/48 weeks >75 kg - 1200 mg/day in 2 divided doses/48 weeks B: (low dose) Ribavirin  <75 kg - 600 mg/day/48 weeks >75 kg - 800 mg/day in 2 divided doses/48 weeks | None | | Age 18–70 years Biopsy proved (within <12 months) chronic hepatitis C with advanced fibrosis/cirrhosis (Ishak stage F4–F6 <7 Child–Pugh points No previous antiviral treatment Elevated alanine aminotransferase (ALT; on >2 occasions within >6 months) Serum HCV RNA positive Hemoglobin >11 g/dL Neutrophil count >1500/lL Platelet count >75 000/lL Serum creatinine <1.5 times upper limit of normal Normal fasting glucose (or <8 μmol/L provided HbA1c <8.5%) Hbs-antigen negative antinuclear antibodies <1:160 Normal thyroid stimulating hormone Normal alpha-fetoprotein Focal lesions ruled out by ultrasound (within 1 month of study entry) | | Concomitant liver disease Ongoing substance abuse including alcohol (>80 g/day) Hepatocellular carcinoma Clinically relevant disorders of other organs/systems Pregnancy or lactation Refusal to practice effective contraception during treatment/followup Immunomodulatory treatment within 6 months or treatment with any investigational drug within 30 days of study entry | | | NR/126/ 126/124 | A vs. B Age - Median: 47 vs. 47 years  Female: 30% vs. 40%  Race: NR | A vs. B Genotype 1 – 30/64(47%) vs. 25/60(42%)  Genotype 2 – 11/64(17%) vs. 7/60(12%) Genotype 3 - 18/64(28%) vs. 24/60(40%) Genotype 4 - 4/64(6%) vs. 3/60(4%)   Histologic stage (Ishak): 3 - 3/64(5%) vs. 4/60(7%)  4 - 26/64(41%) vs. 18/60(30%)  5 - 19/64(30%) vs. 21/60(35%)  6 - 14/64(22%) vs. 13/60(22%)  Cirrhosis: 57% vs. 52%  Minimal or no fibrosis: 6% vs. 2%  100% Treatment naïve | |

| **Author, Year Country Study Name Quality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Helbling, 200651 Switzerland  Continued | Followup visits at 24 weeks post-treatment | A vs. B ETR: NR  SVR: 33/64(52%) vs. 23/60(38%), p=0.153 | NR | A vs. B ETR: NR  SVR:  Fibrosis (Ishak): F4 - 15/26(58%) vs. 6/18(33%) F5-6 - 14/33(42%) vs. 14/34(41%)  Genotype 1/4 - 11/34(32%) vs. 9/28(32%) Genotype 2/3 – 21/29(72%) vs. 14/31(45%) | NR | A vs. B Discontinuation: 15/64 (23%) vs. 16/60 (27%); p=NS Discontinuation (due to AE): 6/64(9%) vs. 9/60(15%); p=NS Overall withdrawals: 18/64(28%) vs. 23/60(38%); p=NS Deaths: 0/64(0%) vs. 2/60(3%); p=NS Severe Adverse Events: 9/64(14%) vs. 11/60(18%); p=NS  Adverse events: Psychiatric - 1/64(2%) vs. 4/60(7%); p=NS Neurologic - 3/64 (5%) vs. 1/60(2%); p=NS Infectious - 1/64(2%) vs. 2/60(3%); p=NS Neoplastic - 2/64 (3%) vs. 1/60(2%); p=NS Skin - 0/64(0%) vs. 1/60(2%); p=NS Endocrine and Metabolism - 0/64(0%) vs. 1/60(2%); p=NS Eye - 1/64(2%) vs. 0/60(0%); p=NS Gastrointestinal - 0/64(0%) vs. 1/60(2%); p=NS Cardiovascular - 1/64(2%) vs. 0/60(0%); p=NS | NR |

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| **Author, Year Country Study Name Quality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **Age Sex Race** | **Genotype Severity of Liver Disease Proportion Treatment-Naïve** |
| Jacobson, 200752 USA (236 practice sites nation-wide)  Pegylated interferon alfa-2b and Weight-Based or Flat-Dose Ribavirin in Chronic Hepatitis C Patients: A Randomized Trial  Jacobson, 200753 (African-American sub-group)  USA (236 practice sites nation-wide)  Impact of Weight-based Ribavirin with Pegylated interferon alfa-2b in African-Americans with Hepatitis C Virus Genotype 1  Overall Quality: Fair | A: Pegylated interferon alfa-2b 1.5 µg/kg 1x/week/24 - 48 weeks depending on genotype B: Pegylated interferon alfa-2b 1.5 µg/kg 1x/week/24 - 48 weeks depending on genotype | A: Ribavirin 800 mg/day 24- 48 weeks depending on genotype B: Ribavirin 800-1400 mg/day for 24-48 weeks depending on genotype  <65kg - Ribavirin 800 mg/week/48 weeks 65-85 kg - Ribavirin 1000 mg/week/48 weeks >85-105 kg - Ribavirin 1200 mg/week/48 weeks >105 kg but <125 kg - Ribavirin 1400 mg/week/48 weeks | None | Treatment-naive chronic hepatitis C patients 18 to 70 years old Body weight less than 125 kg Treatment-naive adult patients with HCV RNA levels detectable by (PCR)/branched DNA assay Compensated liver disease Liver biopsy showing HCV infection within 36 months prior to screening Elevated ALT at least once during the 6 months prior to screening Alpha-fetoprotein level of <100 ng/mL in the year preceding entry | Positive test result for hepatitis B surface antigen or human immunodeficiency virus (HIV) | Paper 1: NR/ NR/ 5519/ 4913  Paper 2: 4913/ 387/ 387/ 387 (sub population from Jacobson , 2007a) | A vs. B Age - Mean: - 45.8 vs. 45.8 years  Female - 37.7% vs. 36.2%  Race: White - 80.7% vs. 78.8% Non White - 19.3% vs. 21.2%  Paper 2: Race:  100% Non White (African-American) | A vs. B Genotype 1 - 1512/2469 (61.2%) vs. 1506/2444 (61.6%) Genotype 2 - 499/2469 (20.2%) vs. 525/2444 (21.5%) Genotype 3 - 421/2469 (17.1%) vs. 386/2444 (15.8%) Genotype 4/5/6 - 33/2469 (1.3%) vs. 23/2444 (0.9%) Genotype viral load >600,000 IU/mL - 1232/2469 (49.9%) vs. 1125/2444 (46.0%) METAVIR stage:  F0–F2 - 1729/2469 (70.0%) vs. 1709/2444 (69.9%) F3 - 486/2469 (19.7%) vs. 489/2444 (20.0%) F4 - 254/2469 (10.3%) vs. 246/2444 (10.1%) ALT abnormal: 2119/2469 (85.8%) vs. 2105/2444 (86.1%) HCV viral load (> 600,000 IU/mL): 1232/2469(49.9%) vs. 1125/2444(46%)  100% Treatment naive Paper 2: (African-Americans)  Genotype 1: 100% HCV viral load > 600,000 IU/mL - 119/202(59%) vs. 116/185(63%) METAVIR stage F3-F4 (%) - 60/202(30%) vs. 58/185(31%) Cirrhosis: 10% vs. 10%  Minimal or no fibrosis: NR  100% Treatment naïve |

| **Author, Year Country Study Name Quality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Jacobson, 200752 USA (236 practice sites nation-wide)  Jacobson, 200753 (African-American subgroup)  USA (236 practice sites nation-wide)  Continued | Followup visits at 24 weeks after completion of treatment | A vs. B ETR: 1193/2102(56.8%) vs. 1255/2121(59.2%), p= 0.082   SVR: 852/2102(40.5%) vs. 938/2121(44.2%), p=0.010 | A vs. B 65-85 kg: 43.8% vs. 45.2% 85-105 kg: 38.8% vs. 42% >105 kg: 33.5% vs. 47.3%   African-Americans Genotype 1: 19/188(10.1%) vs. 36/174(20.7%), p=0.006 | A vs. B Genotype1: 337/1305 (29%) vs. 447/1313 (34%); p=0.005 Genotype 2/3: 462/777 (60%) vs. 479/775 (62%); p=0.252  Genotype 1 High Viral Load - 199/744(26.7%) vs. 246/789(31.2%), p=0.056  Genotype 1 Low Viral Load - 149/427(34.9%) vs. 151/381(39.6%); p=0.164 | NR | A vs. B Discontinuation: 354/2444(14.5%) vs. 369/2469(14.9%); p=NS Overall withdrawals: 913/2444(37.3%) vs. 895/2469(36.2%); p=NS Death: 5/2444(<1%) vs. 9/2469(<1%); p=NS Serious Adverse Event: 279/2444(11.4%) vs. 287/2469(11.6%); p=NS  Adverse events: Cardiovascular – 136/2444(5.6%) vs.162/2469(6.6%); p=NS Psychiatric - 1685/2444(68.9%) vs. 1667/2469(67.5%); p=NS Anemia - 473/2444(19.4%) vs. 721/2469(29.2%); p<0.001  Paper 2 (African Americans): Discontinuation: 85/202(42%) vs. 68/165(41%); p=NS Overall withdrawals: 35/202(17% ) vs. 30/165(18%); p=NS Deaths: NR Severe Adverse Events: NR Adverse events: Nadir hemoglobin- <10 g/dL - 30/202(15%) vs. 37/185(20%); p=NS  <8.5 g/dL - 2/202(1%) vs. 8/185(4%); p=0.04 RBV dose-reduction - 53/202(26%) vs. 69/185(37%);p=0.02 Nadir Absolute Neutrophil Count- <750 cells/mm3 - 56/202(28%) vs. 44/185(24%); p=NS <500 cells/mm3 - 10/202(5%) vs. 15/185(8%); p=NS Nadir platelets: <100 x 103 cells/mm3 - 30/202(15%) vs. 21/185(11%); p=NS <50 x 103 cells/mm3 - 2/202(1%) vs. 2/185(1%); p=NS | Schering-Plough Corp., Kenilworth, NJ |

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| **Author, Year Country Study Name Quality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **Age Sex Race** | **Genotype Severity of Liver Disease Proportion Treatment-Naïve** |
| Kawaoka,  200954 Japan  Dose comparison study of pegylated interferon-α-2b plus ribavirin in naïve Japanese patients with hepatitis C virus genotype 2: A randomized clinical trial  Overall Quality: Fair | A: Pegylated interferon alpha-2a 1.0 μg/kg/week/24 weeks B: Pegylated interferon alpha-2a 1.5 μg/kg/week/24 weeks | A: Ribavirin  60 kg - 600 mg/week/24 weeks >60 kg-<80 kg - 800 mg/week/24 weeks  >80 kg - 1000 mg/week/24 weeks B: Ribavirin  60 kg - 600 mg/week/24 weeks >60 kg-<80 kg - 800 mg/week/24 weeks  >80 kg - 1000 mg/week/24 weeks | None | Patients with chronic hepatitis C  Age >20 years Treatment naïve Genotype 2 | Patients treated with Shosaiko-to, a Japanese herbal medicine considered to improve liver function  Patients with autoimmune hepatitis Patients with a history of hypersensitivity to Pegylated Interferon-alpha-2a or other interferons History of hypersensitivity to biological products, such as vaccines Decompensated liver cirrhosis (LC)  Hepatocellular carcinoma (HCC) or malignant tumors in other tissues History of severe psychosis, such as being severely depressed and/or suicidal  Women who were pregnant or lactating or who were suspected of being pregnant Patients judged by the investigator not to be appropriate for inclusion | NR/ 55/ 53/ 53 | A vs. B Age - Median: 57 vs. 55 years  Female: 65% vs. 44%  Race: NR (study conducted in Japan) | A vs. B Genotype 2a: 13/26(50%) vs. 13/27(48%) Genotype 2b: 13/26(50%) vs. 14/27(52%)  Histological stage (Desmet): F0 - 1/26(4%) vs. 0/27(0%) F1 - 14/26(51%) vs. 13/27(48%) F2 - 8/26(31%) vs. 9/27(33%) F3 - 3/26(12 %%) vs. 5/27(19%)  Cirrhosis: None  Minimal or no fibrosis: 55% vs. 48%  100% Treatment naive |

| **Author, Year Country Study Name Quality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Kawaoka, 200954 Japan  Continued | 24 weeks following treatment completion | A vs. B ETR: 23/26(88.5%) vs. 25/27(92.6%), p=0.13  SVR: 10/26(38.5%) vs. 20/27(74.1%), p=0.013 | NR | NR | NR | A vs. B Overall withdrawals/drop-out: 2/26(7.2%) vs. 2/27(7.6%); p=NS Discontinuation (pre-mature withdrawal of treatment due to AE): 3/26(11.5%) vs. 2/27(7.4%); p=NS   Depression - 1/26(3.8%) vs. 0/27(0%); p=NS  Fatigue - 1/26(3.8%) vs. 1/27(4%); p=NS  Excitability - 0/26(0%) vs. 1/27(4%); p=NS Deaths: NR Severe Adverse Events: NR  Adverse events (leading to dose-reduction): Thrombocytopenia - 1/26(4%) vs. 0/27(0%); p=NS Fatigue - 1/26(4%) vs. 3/27(11%); p=NS Neutropenia - 0/26(0%) vs. 1/27(4%); p=NS Anemia - 15/26 (57.7%) vs. 10/27 (37%); p=NS Reduced Ribavirin - 21/26 (80.7%) vs. 22/27(81.5%); p=NS | NR |

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| **Author, Year Country Study Name Quality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **Age Sex Race** | **Genotype Severity of Liver Disease Proportion Treatment-Naïve** |
| Krawitt, 200655 USA (New York/New England)  A Study of Low Dose Pegylated interferon Alpha-2b with Ribavirin for the Initial Treatment of Chronic Hepatitis C  Overall Quality: Fair | A: (low dose) Pegylated interferon alpha-2b 50 μg/week/24 weeks (treatment continued for additional 24 weeks if HCV RNA undetectable by PCR at week 24) B: (standard dose) pegylated interferon alpha-2b  <75 kg - 100 μg/week/24 weeks ≥75kg - 150 μg/week/24 weeks  (treatment continued for additional 24 weeks if HCV RNA undetectable by PCR at week 24) | A: Ribavirin 1000 mg/day/24 weeks  (treatment continued for additional 24 weeks if HCV RNA undetectable by PCR at week 24) B: Ribavirin 1000 mg/day/24 weeks (treatment continued for additional 24 weeks if HCV RNA undetectable by PCR at week 24) | None | Age > 18 years older Detectable serum hepatitis C virus (HCV) RNA Treatment naive Liver biopsy consistent with the diagnosis of chronic hepatitis C, performed not longer than 5 yr prior to entry, with histological interpretation performed by pathologists at the study site locations Chronic hepatitis alone (F0) Chronic hepatitis with fibrosis, including bridging fibrosis (F1–F3) Chronic hepatitis with cirrhosis (F4) | Positive serum hepatitis B surface antigen Any chronic liver disease other than chronic hepatitis C Hemoglobinopathies Evidence of hepatic decompensation(ascites, encephalopathy, gastrointestinal bleeding secondary to portal hypertension) Other conditions that could interfere with participation in the protocol - (i.e. coronary artery disease, uncontrolled hypertension, clinically significant retinal abnormalities, pregnancy, nursing, severe preexisting psychiatric disorders Active substance dependency within 6 months of screening for entry into the study Methadone maintenance (unless a program of continual testing was in use) History of organ transplantation Participation in any other clinical trial or use of another investigational drug within 30 days of entry | NR/NR/ 314/301 | A vs. B Age:  > 50 years - 18% vs. 19%  Female - 38% vs. 36%  Race:   Non White - 4.6% vs. 3.1% | A vs. B Genotype 1 - 109/152(71.7%) vs. 119/162(73.5%) Genotype 2/3 - 43/152(28.3%) vs. 43/162(26.5%)  Histology Fibrosis - 80/152(52.6%) vs. 92/162(56.8%) Cirrhosis - 26/152(17.1%) vs. 17/162(10.5%)  Baseline HCV RNA: < 2 x 106 copies/ml - 67/152(44.1%) vs. 86/162(40.7%) > 2 x 106 copies/ml - 85/152(55.9%) vs. 96/162(59.3%)  100% Treatment naive |

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| Krawitt, 200655 USA (New York/New England)  Continued | Followup visits at 24 weeks Post-treatment | A vs. B ETR: NR  SVR: 50/152(33%) vs. 73/162(45%), p=0.02 | A vs. B ETR: NR  SVR:  Age: ≤ 40 years - 13/33(39%) vs. 18/38(47%), p= 0.63 > 40 - ≥ 50 years - 28/91(31%) vs. 40/93(43%), p= 0.09 > 50 years - 9/28 (32%) vs. 15/31 (48%), p= 0.29  Male: 29/94 (31%) vs. 44/110 (40%); p=0.14 Female - 21/58(36%) vs. 29/52(56%), p=0.06  Race: Caucasian - 50/145 (34%) vs. 70/157 (45%), p= 0.08 African-American - 0/6 (0%) vs. 3/4 (75%), p= 0.03 Hispanic/Other - 0/1 (0%) vs. 0/1 (0%), p= 1.00  Weight:  < 75 kg - 20/50 (40%) vs. 24/42 (57%), p= 0.14 ≥ 75 kg - 30/102 (29%) vs. 49/120 (41%), p= 0.09 | A vs. B ETR: NR  SVR:  HCV Genotype:  Genotype 1 - 26/109 (24%) vs. 45/119 (38%), p= 0.03 Genotype 2/3 - 24/43 (56%) vs. 28/43 (65%), p= 0.51  Baseline HCV RNA:  ≤ 2×106 copies/ml - 19/67 (28%) vs. 37/66 (56%), p= 0.002 > 2×106 copies/ml - 31/85 (36%) vs. 36/96 (38%), p= 1.00  Histology: No fibrosis or cirrhosis: 17/46 (37%) vs. 29/53 (55%); p=0.11 Fibrosis - 27/80 (34%) vs. 39/92 (42%), p= 0.27 Cirrhosis - 6/26 (23%) vs. 5/17 (29%), p= 0.73 | NR | A vs. B Total Discontinuation: 9/147(6%) vs. 28/154(18%); p=0.0015 Discontinuation due to AE: 5/147(3%) vs. 14/154(9%); p=0.04 Overall withdrawals: NR Deaths: NR Severe Adverse Events: NR | Integrated Therapeutics Group (Schering-Plough) |

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| **Author, Year Country Study Name Quality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **Age Sex Race** | **Genotype Severity of Liver Disease Proportion Treatment-Naïve** |
| Manns, 200156 US & UK  Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial  Overall Quality: Fair | A: Pegylated interferon alfa-2b 1·5 g/kg/4 weeks  followed by Pegylated interferon 0·5 g/kg/week/44 weeks  B: interferon alfa-2b 3 million units/3x week/48 weeks | A: (weight-based) Ribavirin 1000–1200 mg/day/48 weeks 75 kg > 1000 mg 75 kg < 1200 mg  B: (weight-based) Ribavirin 1000–1200 mg/day/48 weeks 75 kg > 1000 mg 75 kg < 1200 mg | NA | Eligible patients were previously untreated adults who had HCV RNA detectable in serum by PCR, who had undergone a liver biopsy within 1 year before entry that was consistent with chronic hepatitis, and who had high serum values of alanine aminotransferase (above the upper limit of normal >43 IU/L for men, >34 IU/L for women) with minimum hematological and biochemical values of: hemoglobin 120 g/L for women and 130 g/L for men; white-blood-cell count 3 109/L; neutrophil count 1·5 109/L; platelet count 100 109/L; and bilirubin, albumin, and creatinine within normal limits. | Patients were excluded if they had decompensated cirrhosis, serum-fetoprotein concentration of more than 50 g/L, HIV infection, previous organ transplantation, other causes of liver disease, pre-existing psychiatric disease, seizure disorders, cardiovascular disease, hemoglobinopathies, hemophilia, poorly controlled diabetes, or autoimmune type disease, or if they were unable to use contraception. | NR/2316/1530/1530 | **A vs. B:**   Age (Mean): 44 vs. 43 years Female: 168/514(33%) vs. 169/505(33%) Race: NR | **A vs. B** Genotype 1: 68% vs. 68% Genotype 2/3: 30% vs. 29% Genotype 4, 5, or 6: 2% vs.3%  Histology Mean (SD) baseline Knodell inflammatory score: 7·9 (2·3) vs. 7·8 (2·5)  Bridging fibrosis/cirrhosis: 146/491(30%) vs. 132/468(28%)  Treatment naive: 100% |

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| Manns, 200156 US & UK  Continued | 24 weeks following treatment completion | | SVR: 333/511(65%) vs. 289/514(56%) vs. 271/505(54%), p<0·001 (A vs. B), p=0·41 (A vs. C) | | NR | | | **A vs. B vs. C:** SVR: Genotype 1: 42% (145/348) vs. 34% (118/349) vs. 33% (114/343), p=0·02 (A vs. B), p=0·94(A vs C) Genotype 2/3: 82% (121/147) vs. 80% (122/153) vs. 79% (115/146), p=0·46(A vs. B), p=0·89 (A vs. C) Genotype 4/5/6: 50% (8/16) vs. 33% (4/12) vs. 38% (6/16), p=0·72 (A vs B), p>0·99 (A vs. C) SVR by baseline HCV: >2 106/mL: 42% (149/351) vs. 42% (144/345) vs. 42% (145/344)  2 106/mL: 78% (125/160) vs. 59% (100/169) vs. 56% (90/161)  SVR by degree of fibrosis: No/minimal fibrosis - 57% (189/333) vs. 51% (175/345) vs. 49% (164/336) Bridging fibrosis/cirrhosis - 44% (60/136) vs. 43% (63/146) vs. 41% (54/132) | | NR | A vs B vs. C: Overall withdrawals: NR  Withdrawals for adverse events: 42/511 vs. 36/514 vs. 34/505 Serious adverse events: NR  Deaths: NR  Adverse Events: Anemia: 9/511 vs. 12/514 vs. 13/505 Neutropenia: 18/511 vs. 10/514 vs. 8/505 Asthenia 18/511 vs. 16/514 vs. 18/505 Fatigue 64/511 vs. 62/514 vs. 60/505 Fever 46/511 vs. 44/514 vs. 33/505 Headache 62/511 vs. 58/514 vs. 58/505 Rigors 48/511 vs. 45/514 vs. 41/505 Weight decrease 29/511 vs. 17/514 vs. 20/505 Dizziness 21/511 vs. 21/514 vs. 17/505 Arthralgia 34/511 vs. 34/514 vs. 28/505 Musculoskeletal pain 21/511 vs. 17/514 vs. 19/505 Myalgia 56/511 vs. 48/514 vs. 50/505 Anorexia 32/511 vs. 29/514 vs. 27/505 Diarrhea 22/511 vs. 16/514 vs. 17/505 Nausea 43/511 vs. 36/514 vs. 33/505 Vomiting 14/511 vs. 14/514 vs. 12/505 Concentration impairment 17/511 vs. 16/514 vs. 21/505 Depression 31/511 vs. 29/514 vs. 34/505 Insomnia 40/511 vs. 40/514 vs. 41/505 Irritability 35/511 vs. 34/514 vs. 34/505 Coughing 17/511 vs. 15/514 vs. 13/505 Dyspnea 26/511 vs. 23/514 vs. 24/505 Alopecia 36/511 vs. 29/514 vs. 32/505 Pruritus 29/511 vs. 26/514 vs. 28/505 Rash 24/511 vs. 22/514 vs. 23/505 Dry skin 24/511 vs. 18/514 vs. 23/505 Injection-site inflammation 25/511 vs. 27/514 vs. 18/505 Injection-site reaction 58/511 vs. 59/514 vs. 36/505 | Schering Plough Research Institute, Kenilworth, NJ, and clinical research centre grants from Massachusetts General Hospital (MO1-RR01066), Scripps Clinic  (MO1-RR00833), and University of Florida (5MO1-RR00082). |

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| **Author, Year Country Study Name Quality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **Age Sex Race** | **Genotype Severity of Liver Disease Proportion Treatment-Naïve** |
| Meyer-Wyss, 200657 Switzerland  Comparison of two PEG-interferon alpha-2b doses (1.0 or 1.5µg/kg) combined with ribavirin in interferon-naïve patients with chronic hepatitis C and up to moderate fibrosis  Overall Quality: Poor | A: Pegylated-interferon alpha-2b 1.0 μg/kg/week/24-48 depending on genotype B: Pegylated-interferon alpha-2b 1.5 μg/kg/week/24-48 depending on genotype | A: Ribavirin 800mg/day/24-48 depending on genotype B: Ribavirin 800mg/day/24-48 depending on genotype | None | Treatment-naive patients Aged 18–65 years Biopsy-proven chronic hepatitis C within <12 months Up to moderate fibrosis (METAVIR score <F2) with elevated alanine aminotransferase levels (ALT; on at least two occasions, at least 6 months apart)  HCV-RNA positive serum | Subjects participating in any study within 30 days prior to entry into the trial  Pregnant or nursing women Positive human immunodeficiency virus (HIV)status Liver disease other than chronic hepatitis C Elevated levels of fasting blood glucose Abnormal values of thyroid stimulating hormone Hemophilia or Hemoglobinopathy  Any known pre-existing medical condition that could interfere with the patient’s participation and completion of the study including:  History of severe psychiatric disorders Central nervous system trauma/active seizure disorders Significant cardiovascular Pulmonary, or retinal disorders Clinically manifested gout Substance abuse Chronic systemic administration of steroids/other immunosuppressants Immunologically mediated disease. | NR/NR/ 227/219 | A vs. B Age - Median: 39 vs. 42 years  Female: 43% vs. 28%  Race: NR | A vs. B Genotype 1 - 49/113(43%) vs. 64/106(60%) Genotype 2 - 14/113(12%) vs. 10/106(%) Genotype 3 - 41/113(36%) vs. 26/106(9%) Genotype 4 - 9/113(8%) vs. 6/106(6%)  Histological stage (METAVIR score): 0 - 21/113(19%) vs. 13/106(12%)  1 - 44/113(39%) vs. 39/106(37%)  2 - 48/113(42%) vs. 54/106(51%)  Cirrhosis: None  Minimal of no fibrosis: NR  100% Treatment naive |

| **Author, Year Country Study Name Quality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Meyer-Wyss , 200657 Switzerland  Continued | Followup visits at 4 and 24 weeks post-treatment | A vs. B ETR: NR  SVR: 61/113(53%) vs. 56/106(53%), p= ns | NR | A vs. B ETR: 17/39(49%) vs. 23/49(47%)  SVR: Genotype 1/4: 22/58 (38%) vs. 27/70 (39%), p= ns  Genotypes 2/3: 39/55 (71%) vs. 29 /36 (81%), p = ns  >800K IU/mL: 28/48 (58%) vs. 40/69 (43%); p=NS <800 IU/mL: 34/65 (52%) vs. 40/69 (58%): p=NS | NR | A vs. B  Discontinuation: 14/115(12%) vs. 28/112(25%); p=0.01 Deaths: 0/115(0%) vs. 1/112(0%); p=NS Life-threatening Adverse Events: 4/115(3%) vs. 9/112(9%); p=NS Severe Adverse Events: 62/115(54%) vs. 59/112(53%); p=NS  Withdrawals due to AE: 22/115 (19%) vs. 34/112 (30%); p=0.05 Adverse events (only body systems listed with at least 10% of patients reporting): Thrombocytopenia: 1/115(1%) vs. 1/112(1%); p=NS Leukopenia: 9/115(8%) vs. 5/112(4%); p=NS Neutropenia: 20/115(17%) vs. 18/112(16%); p=NS Hemolytic anemia: 3/115(3%) vs. 3/112(3%); p=NS Blood and lymphatic system disorders - 44/115(38.3%)vs. 41/112 (36.6%); p=NS General disorders and administration site conditions - 112/115(97.4%) vs. 108/112(96.4%); p=NS Gastrointestinal disorders - 81/115(70.4%)vs. 84/112(75.0%); p=NS Metabolism and nutrition disorders -16/115(13.9%) vs. 29/112(25.9%); p=0.02 Musculoskeletal and connective tissue disorders - 27/115(23.5%) vs. 33/112(29.5%); p=NS Nervous system disorders - 70/115(60.9%) vs. 80/112(71.4%); p=NS Psychiatric disorders - 71/115(61.7%) vs. 76/112(67.9%); p=NS Respiratory, thoracic and mediastinal disorders  18/115(15.7%) vs. 24/112(21.4%); p=NS Skin and subcutaneous disorders - 83/115(72.2%) vs. 76/112(67.9%); p=NS | Essex Chemie AG, Lucerne |

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| **Author, Year Country Study Name Quality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **Age Sex Race** | **Genotype Severity of Liver Disease Proportion Treatment-Naïve** |
| Mimidis, 200658 Greece  Hepatitis C virus survival curve analysis in naïve patients treated with Pegylated interferon alpha-2b plus ribavirin. A randomized controlled trial for induction with high doses of Pegylated interferon and predictability of sustained viral response from early virologic data  Overall Quality: Poor | A. Pegylated interferon alfa-2b 3.0 mcg/kg weekly for 12 weeks followed by 1.5 mcg/kg weekly for 36 weeks B. Pegylated interferon alfa-2b 1.5 mcg/kg weekly for 48 weeks | A. 800-1200 mg daily (11 mg/kg) B. 800-1200 mg daily (11 mg/kg) | NA | Treatment-naïve HCV RNA detected in serum Liver biopsy consistent with chronic hepatitis within 6 months before enrollment Elevated ALT at entry and at least once in 6 months before screening | HBV HIV coinfection Hemochromatosis Alpha-1 anti-trypsin deficiency Wilson's disease Autoimmune hepatitis Alcohol drug or obesity induced liver disease Substance abuse Any known pre-existing condition that could interfere with patient's participation Creatinine >1.5 mg/dL  Neutrophils <1000/mL3 Platelets <50K/mL3 Hemoglobin <11 g/dL | NR/NR/ 188/120 | A vs. B Age mean: NR Sex: 36% vs. 38% non White: NR | A vs. B genotype 1/4: 46% vs. 52% Treatment-naïve: all Fibrosis: NR  Cirrhosis: NR HCV RNA> 800k IU/mL: NR |

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| Mimidis, 200658 Greece  Continued | Week 72 | A vs. B ETR: NR  SVR: 38/89 (42.7%) vs. 47/87 (54%) | NR | A vs. B Genotype 1: 9/35 (25.7%) vs. 18/40 (45%); p=NS Genotype 2/3: 23/48 (47.9%) vs. 25/42 (59.5%); p=NS Genotype 4: 6/6 (100%) vs. 4/5 (80%); p=NS | NA | NR | NR |

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| **Author, Year Country Study Name Quality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **Age Sex Race** | **Genotype Severity of Liver Disease Proportion Treatment-Naïve** |
| Reddy, 201059 International, 14 countries  Induction pegylated interferon alfa-2a and high dose ribavirin do not increase SVR in heavy patients with HCV genotype 1 and high viral loads  Overall Quality: Fair | A. Pegylated interferon alpha-2a 360 mcg weekly for 12 weeks then 180 mcg weekly for 36 weeks B. Pegylated interferon alpha-2a 360 mcg/weekly for 12 weeks then 180 mcg weekly for 36 weeks C. Pegylated interferon alpha-2a 180 mcg weekly for 48 weeks D. Pegylated interferon alpha-2a 180 mcg weekly for 48 weeks | A. 1400 - 1600 mg/day for 48 weeks depending on weight B. 1200 mg/day for 48 weeks C. 1400 - 1600 mg/day for 48 weeks depending on weight D. 1200 mg/day for 48 weeks | NA | Treatment-naïve Aged 18 years or older Weight > 85 kg HCV genotype 1 infection HCV RNA > 400k IU/mL Liver biopsy in past 24 months consistent with chronic hepatitis C | coinfection with HBV, HAV, or HIV Chronic liver disease of other origin Current or past history of chronic systemic disease including severe psychiatric disease Increased baseline risk of anemia Neutrophils <1500/mL3 Platelets <90K/mL3 Hemoglobin<12 g/dL in men or <13 g/dL in women Creatinine >1.5 times upper limit of normal Pregnant or breastfeeding women and male partners | NR/NR/ 1175/1145 | A vs. B vs. C vs. D Age mean: 46 vs. 46 vs. 45 vs. 46 Female: 19% vs. 24% vs. 22% vs. 19% non White: 14% vs. 13% vs. 19% vs. 13% | A vs. B vs. C vs. D genotype 1: all Treatment-naïve: all Bridging fibrosis/cirrhosis: 12% vs. 8% vs. 10% vs. 12% HCV RNA >800k IU/mL: 86% vs. 83% vs. 84% vs. 82% |

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| Reddy, 201059 International, 14 countries  Continued | Week 72 | A vs. B vs. C vs. D ETR: NR  SVR: 156/383 (40.7%) vs. 166/382 (43.5%) vs. 81/189 (42.9%) vs. 72/191 (37.7%); (p=NS for all comparisons) | A vs. B vs. C vs. D (counts not reported) Weight <95 kg: 44% vs. 46% vs. 44% vs. 49% Weight >95 kg: 38% vs. 41% vs. 41% vs. 29% | A vs. B vs. C vs. D (counts not reported) Steatosis score <5%: 42% vs. 48% vs. 48% vs. 47% Steatosis score >5%: 36% vs. 30% vs. 32% vs. 13% | NA | A vs. B vs. C vs. D Overall withdrawals: 117/383 (31%) vs. 109/382 (29%) vs. 53/189 (28%) vs. 54/191 (28%); A vs. C p=NS; B vs. D p=NS Withdrawals for adverse events: 47/383 (12%) vs. 40/382 (10%) vs. 17/189 (9%) vs. 22/191 (12%); A vs. C p=NS; B vs. D p=NS Serious adverse events: 39/383 (10%) vs. 36/382 (9%) vs. 20/189 (11%) vs. 22/191 (12%); A vs. C p=NS; B vs. D p=NS Deaths: 2/383 (<1%) vs. 2/382 (<1%) vs. 3/189 (1%) vs. 1/191 (<1%); A vs. C p=NS; B vs. D p=NS Pyrexia: 205/383 (54%) vs. 176/382 (46%) vs. 78/189 (41%) vs. 83/191 (43%); A vs. C p=NS; B vs. D p=NS Fatigue: 182/383 (48%) vs. 185/382 (48%) vs. 102/189 (54%) vs. 66/191 (35%); A vs. C p=NS; B vs. D p=NS Headache: 168/383 (44%) vs. 152/382 (40%) vs. 76/189 (76%) vs. 75/191 (39%); A vs. C p=0.006; B vs. D p=0.002 Chills: 132/383 (34%) vs. 122/382 (32%) vs. 55/189 (29%) vs. 42/191 (22%); A vs. C p=NS; B vs. D p=0.001 Myalgia: 113/383 (30%) vs. 98/382 (26%) vs. 45/189 (24%) vs. 46/191 (24%); A vs. C p=NS; B vs. D p=NS Arthralgia: 89/383 (23%) vs. 88/382 (23%) vs. 49/189 (26%) vs. 50/191 (26%); A vs. C p=NS; B vs. D p=NS Depression: 58/383 (15%) vs. 72/382 (19%) vs. 36/189 (19%) vs. 32/191 (17%); A vs. C p=NS; B vs. D p=NS Hemoglobin <8.5 g/dL: 22/383 (6%) vs. 9/382 (2%) vs. 12/189 (6%) vs. 6/191 (3%); A vs. C p=NS; B vs. D p=NS | Roche |

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| Reddy, 201059 International, 14 countries  Continued |  |  |  |  |  | Neutrophils <500/mL3: 26/383 (7%) vs. 25/382 (7%) vs. 10/189 (5%) vs. 9/191 (5%); A vs. C p=NS; B vs. D p=NS Platelets <20K/mL3: 3/383 (1%) vs. 0/382 (0%) vs. 0/189 (0%) vs. 3/191 (2%); A vs. C p=NS; B vs. D p=NS |  |

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| Roberts, 200960 Australia  Impact of high-dose Pegylated interferon alfa-2a on virologic response rates in patients with hepatitis C genotype 1: a randomized controlled trial  Overall Quality: Fair | A. Pegylated interferon alfa-2a 360 mcg weekly for 12 weeks followed by 180 mcg for 36 weeks (48 weeks total) B. Pegylated interferon alfa-2a 180 mcg weekly for 48 weeks | A. 1000-1200 mg/day for 48 weeks B. 1000-1200 mg/day for 48 weeks | NA | Treatment naïve Ages 18 -75 years HCV genotype 1 infection HCV RNA >600 IU/mL Elevated ALT Compensated liver disease (Child-Pugh score <7) Histologic findings consistent with chronic hepatitis on liver biopsy within last 36 months  \*Protocol modified during study to remove ALT, pretreatment biopsy, and compensated cirrhosis inclusion/exclusion requirements | HBV HIV coinfection History of decompensated liver disease Evidence of hepatocellular carcinoma Liver disease of other origin Therapy with systemic antiviral, antineoplastic, or immunomodulatory agents within 6 months Pregnancy or breast feeding and male partner of women  Neutrophils <1500/mL3 Hemoglobin <12 g/dL in women and <13 g/dL in men Creatinine >1.5 times the upper limit of normal Active severe psychiatric disease Any severe chronic or uncontrolled disease Current or recent drug or alcohol abuse Cirrhosis | NR/NR/ 896/871 | A vs. B Age mean: 44 vs. 43 Female: 31% vs. 35% non White: 18% vs. 17% | A vs. B genotype 1: all Treatment-naïve: all Fibrosis stage 3 or 4: 14% vs. 16% HCV RNA > 800K: 70% vs. 67% |

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| Roberts, 200960  Australia  Continued | 24 weeks after end of treatment (week 72) | A vs. B ETR: 70% vs. 66%; p=0.18  SVR: (230/433) 53% vs. (219/438) 50%; p=0.29 | A vs. B White: 183/355 (52%) vs. 167/365 (46%); p=NS Asian: 40/61 (66%) vs. 40/55 (73%); p=NS Other: 7/17 (41%) vs. 12/18 (67%); p=NS  Male: 149/298 (50%) vs. 134/285 (47%); p=NS Female: 81/135 (60%) vs. 85/153 (56%); p=NS  <40 years: 104/146 (71%) vs. 97/141 (69%); p=NS >40 years: 126/287 (44%) vs. 122/297 (41%); p=NS  Weight <85 kg: 167/294 (57%) vs. 156/297 (53%); p=NS Weight >85 kg: 63/139 (45%) vs. 63/141 (45%); p=NS | A vs. B HCV RNA <800K: 81/125 (65%) vs. 84/138 (61%); p=NS HCV RNA >800K: 147/302 (49%) vs. 132/293 (45%); p=NS  Fibrosis METAVIR stage 3 or 4: 17/60 (28%) vs. 16/67 (24%); p=NS Fibrosis METAVIR stage 0,1,or 2: 148/256 (58%) vs. 134/242 (55%); p=NS | NR | A vs. B Overall withdrawals: 113/433 (26%) vs. 136/438 (31%); p=NS Withdrawals due to adverse events: 44/433 (10%) vs. 36/438 (8%); p=NS Deaths: NR Serious adverse events: 46/433 (11%) vs. 45/438 (10%); p=NS  Headache: 227/433 (52%) vs. 208/438 (47%); p=NS Influenza like illness: 180/443 (42%) vs. 183/438 (42%); p=NS Nausea: 179/433 (41%) vs. 169/438 (39%); p=NS Fatigue: 159/433 (37%) vs. 174/438 (40%); p=NS Myalgia: 114/433 (26%) vs. 97/438 (22%); p=NS Rash: 110/433 (25%) vs. 116/438 (26%); p=NS Depression: 84/433 (19%) vs. 85/438 (19%); p=NS Arthralgia: 82/433 (19%) vs. 76/438 (17%); p=NS Pyrexia: 66/433 (15%) vs. 47/438 (11%); p=NS Chills: 64/433 (15%) vs. 34/438 (8%); p<0.001 Neutropenia: 76/433 (21%) vs. 55/438 (13%); p=0.05 Thrombocytopenia: 17 (4%) vs. 6 (1%); p=0.02 Anemia: 5 (1%) vs. 3 (1%); p=NS | Roche |

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| Sood, 200861 India  Comparison of low-dose pegylated interferon vs. standard high-dose pegylated interferon in combination with ribavirin in patients with chronic hepatitis C with genotype 3: An Indian Experience  Overall Quality: Fair | A: Pegylated-interferon alpha-2b 1.0 μg/kg/week/24 weeks B: Pegylated-interferon alpha-2B 1.5 μg/kg/week/24 weeks | A: Ribavirin 10-12 mg.kg/day/24 weeks B: Ribavirin 10-12 mg.kg/day/24 weeks | None | Aged between 16–70-years-old HCV-RNA positive with genotype 3 Treatment naïve ALT >1.2 x Upper limit of Normal (ULN) at screening and for at least the previous 6 months Liver biopsy–proven chronic HCV within 6 months prior to inclusion | Chronic HCV patients with genotypes other than Genotype 3 Total leukocyte count < 3000 per cubic millimeter Platelet count < 70 000 per cubic millimeter, Hemoglobin level lower than 10 g per deciliter co infection with hepatitis B virus or human immunodeficiency virus,  Alcohol intake exceeding 20 g/day Presence of drug abuse, psychiatric illness, or thyroid dysfunction Pregnancy and lactation  Decompensated liver disease  Evidence of liver disease due to other etiology such as autoimmune or drug-induced hepatitis Serious concurrent medical illnesses (such as malignancy, severe cardiopulmonary disease, or uncontrolled diabetes mellitus)  Inability to give an informed written consent | NR/103/ 103/103 | A vs. B Age - Mean: 43 vs. 37 years  Female: 12% vs. 22%  Race: NR | A vs. B Genotype 3: 100%   (Knodell)  HAI score - Mean (SD): 7.2 (3.15) vs. 4.68(2.12) Fibrosis score - Mean(SD): 2.34(1.27) vs. 1.64(1.29)  Cirrhosis: NR  100% Treatment naïve |

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| Sood, 200861 India  Continued | Followup visits at 24 weeks post-treatment | A vs. B ETR: 72/76(94.7%) vs. 24/27(88.9%), p=0.375  SVR: 60/76(78.9%) vs. 25/27(926%), p=0.145 | NR | NR | NR | A vs. B Overall withdrawals: 1/76 (1.3%) vs. 2/27 (7.4%); p=NS Withdrawals (due to AE): 0/76 vs. 1/27 (4%); p=NS Deaths: NR Severe Adverse Events: NR  Adverse events:  Influenza-like symptoms - 20/27(74.0 %%) vs. 44/76(57.9%); p=NS Malaise or fatigue -10/27(37.0%) vs. 22/76(29.0%); p=NS Nausea or vomiting - 5/27(18.5%) vs. 11/76(14.5%) p=NS Headache - . 4/27 (14.8%) vs. 8/76(10.5%); p=NS Abdominal discomfort - 4/27(14.8%) vs. 8/76 (10.5%); p=NS Diarrhea - . 4/27(14.8%) vs. 9 /76(11.8%); p=NS Grade III or IV laboratory abnormalities  Neutrophils - 3/27(11.1%) vs. 1/76(1.3%); p=0.02 Platelets - 4/27(14.8%) vs. 2/76(2.6%); p=0.02 | NR |