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

| **Author, YearCountryStudy NameQuality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **AgeSexRace** | **GenotypeSeverity of Liver DiseaseProportion Treatment-Naïve** |
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| Abergel, 200647FrancePegylated 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-2bOverall Quality: Fair | A: (standard-dose) Pegylated interferon alpha-2b 1.5 µg/kg 1x/week/48 weeksB: (low-dose) Pegylated interferon alpha-2b 0.75 µg/kg 1x/week/48 weeks | A: Ribavirin 800 mg/day/48weeksB: Ribavirin 800 mg/day/48 weeks | None | Age between 18 and 75 yearsNo previous treatment with IFN and/or ribavirinAlanine aminotransferase (ALT) > upper limit of normal (ULN) at least once during the last 12 monthsPositive serum HCV-RNA using qualitative polymerase chain reaction (PCR) and severe fibrosis on liver biopsy defined by a METAVIR fibrosis stage of F3 orF4 at histological examination of the liver | Recent history of alcohol abuse or IV drug addictionHemoglobin <12 g/dL in women and <13 g/dL in menPlatelets <75 000/lLNeutrophils <1500/lLDecompensated cirrhosis (ascites, variceal hemorrhage encephalopathy)Albumin <30 g/LProthrombin <60%Bilirubin >34 lmol/LHCCChronic hepatitis B infectionHIV infection | NR/210/ 210/203 | A vs. BAge(Mean): 49.3 vs. 51.1 years Female: 36% vs. 32%Race: NR | A vs. BGenotype 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, YearCountryStudy NameQuality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Abergel, 200647FranceContinued | Followup visits at 24 weeks after completion of treatment | A vs. BETR: 59/101(62.8%) vs. 57/102(59.4%)SVR: 50/101(49.5%) vs. 38/102(37.2%) | A vs. BETR: NRSVR: BMI <27 kg/m2 - 35/70 (50.0%) vs. 26/70 (37.1%); p=NSBMI >27 kg/m2 - 10/31 (32.3%) vs. 12/32 (37.5%); p=NSgamma glutamyl transpeptidase (GGT) used as a marker for steatosis:GGT <1.6 ULN - 29/48 (60.4%) vs. 23/48 (47.9%); p=NSGGT >1.6 ULN - 13/50 (26.0%) vs. 13/51 (25.5%); p=NS | A vs. BETR: NRSVR: Genotypes 1, 4, 5, - 15/60(25.0%) vs. 11/65 (16.9%); p=NSGenotype 1 - 12/50 (24.0%) vs. 09/54 (16.7%); p=NSGenotypes 2, 3 - 30/41 (73.2%) vs. 27/37 (73.0%); p=NSViremia <800.000 IU/mL - 25/55 (45.5%) vs. 20/47 (42.5%); p=NSViremia >800 000 IU/mL - 20/44 (45.5%) vs. 17/53 (32.1%); p=NSCirrhosis (F4) - 18/46 (39.1%) vs. 20/58 (34.5%); p=NSSevere fibrosis(F3) - 27/55 (49.1%) vs. 18/44 (40.1%); p=NS | None | A vs. BDiscontinuation - 30/101(31 %) vs. 28/102(27 %)Discontinuation or treatment reduction – 53/101(54%) vs. 37/102(36 %), p <0.03Treatment reduction - 36/101(37%) vs. 13/102(12%), p <0.0002Overall withdrawals - NRDeaths - NRSevere 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 eventsAdverse event - 15/101(16%) vs. 4/102(3%), p <0.01Cytopenia - 20/101(21 %) vs. 9/102(8%), <0.03Anemia - 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=0.054Neutrophils < 750/ µL - 21/101(21%) vs. 8/102(7%), p <0.01Platelets < 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, YearCountryStudy NameQuality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **AgeSexRace** | **GenotypeSeverity of Liver DiseaseProportion Treatment-Naïve** |
| Brady, 201048United StatesInduction pegylated interferon alfa-2b combination with ribavirin in patients with genotype 1 and 4 chronic hepatitis C: a prospective, randomized, multicenter, open-label studyOverall Quality: Fair | A. Pegylated interferon alfa-2b 3.0 mcg/kg/week for 12 weeks followed by 1.5 mcg/kg/week for 36 weeksB. Pegylated interferon alfa-2b 1.5 mcg/kg/week for 48 weeks | A. 800-1400 mg/day for 48 weeksB. 800-1400 mg/day for 48 weeks | NA | Treatment-naïve patientsGenotype 1 or 4Positive HCV antibodies and detectable HCV RNALiver biopsy consistent with viral hepatitis within the past 48 monthsCirrhosis no worse than Child-Pugh Class AHemoglobin >12 g/dL in females and 13 g/dL in malesWhite blood cells >3000Neutrophil >1500Platelet > 65KDirect bilirubin within 20% of upper limits of normalCreatinine within 20% of upper limits of normalAlbumin within normal limits  | Non genotype 1 or 4 HCV infectionDecompensated liver diseaseEvidence of coexisting liver diseaseCoinfection with HIV or HBVHemochromatosisAlpha-1 antitrypsin deficiencyWilson diseaseAutoimmune hepatitisAlcoholic liver diseaseHepatocellular carcinomaPregnancyPsychiatric conditionsSignificant cardiovascular dysfunction within the past 1 yearPoorly controlled diabetes mellitusChronic pulmonary diseaseClinically significant retinal abnormalitiesImmunologically mediated diseasesAny medical condition requiring systemic steroidsActive clinical goutSubstance abuse in the past 6 months | NR/NR/ 623/610 | A vs. BAge mean: 45 vs. 45Female: 50% vs. 50%non White: 32% vs. 28% | A vs. Bgenotype 1: 99% vs. 99%Treatment-naïve: allFibrosis stage 3 or 4: 26% vs. 23%HCV- RNA >800K: 71% vs. 62% |

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| **Author, YearCountryStudy NameQuality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
| Brady, 201048United StatesContinued | 24 weeks following treatment completion | A vs. BETR: 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. BBlack: 13/36 (36.1%) vs. 12/37 (32.4%); p=0.9Hispanic: 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. BOverall withdrawals: 146/299 (48.8%) vs. 133/311 (42.7%); p=0.2Withdrawals for adverse events: NRSerious adverse events: NRDeaths: NRNeutropenia <500: 10/299 (3.4%) vs. 5/311 (1.6%); p=0.261Anemia hemoglobin <10: 50/299 (16.7%) vs. 50/311 (16.1%); p=0.916Thrombocytopenia platelets <50: 3/299 (1.0%) vs. 4/311 (1.3%); p=1.0Pyrexia: 68/299 (22.7%) vs. 80/311 (25.7); p=0.445Myalgia: 114/299 (38.1%) vs. 108/311 (34.7%); p=0.430Rash: 34/299 (11.4%) vs. 58/311 (18.6%); p=0.016Fatigue: 131/299 (43.8%) vs. 156/311 (50.2%); p=0.136Headache: 30/299 (10.0%) vs. 47/311 (15.1%); p=0.077Insomnia: 47/299 (15.7%) vs. 51/311 (16.4%); p=0.906Depression: 55/299 (18.4%) vs. 70/311 (22.5%); p=0.247Nausea: 37/299 (12.4%) vs. 40/311 (12.9%); p=0.953 | Schering Plough |

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| **Author, YearCountryStudy NameQuality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **AgeSexRace** | **GenotypeSeverity of Liver DiseaseProportion Treatment-Naïve** |
| Bronowicki, 200646FranceEffect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirinOverall Quality: Fair | A. Pegylated interferon alfa-2a 180 mcg/week for 48 weeksB. 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 dailyB. Placebo | NA | Treatment naïveAged >18 yearsHCV genotype 1 infectionHCV RNA >600 IU/mLIncreased ALT levels documented 2 times in last 6 monthsLiver biopsy consistent with chronic hepatitis C obtained within 18 months before therapy | chronic liver disease of other etiologyEvidence of decompensationCoinfection with HBV or HIVNeutrophils <1500/mm3platelets <90,000/mm3Hemoglobin level less than 12 g/dL (women) or less than 13 g/dL (men)Risk factor for anemiaSerum creatinine >1.5 times upper limit of numberSevere psychiatric diseaseSignificant comorbid medical conditions | NR/516/ 349/349 | A vs. BAge mean: 44.2 vs. 45.4Female: 43% vs. 43%Non White: NR | A vs. BGenotype 1: allHCV RNA>800,000: 62% vs. 71%Fibrosis score F3 or F4: 27% vs. 28% |

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| **Author, YearCountryStudy NameQuality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
| Bronowicki, 200646FranceContinued | 24 weeks following treatment completion | A vs. BSVR: 93/176 (52.8%) vs. 118/173 (68.2%); p=0.004Hepatitis 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. BOverall withdrawals: NRWithdrawals for adverse events: 3/173 (1.7%) vs. 4/176 (2.3%); p=NSSerious adverse events: 13/173 (7.5%) vs. 12/176 (6.8%); p=NSDeaths: 1/173 (0.5%) vs. 0/176 (0%); p=NSAsthenia: 19/173 (10.6%) vs. 13/176 (7.3%); p=NSHeadache: 7/173 (3.9% ) vs. 6/176 (3.4%); p=NSDepression: 13/173 (7.5%) vs. 16/176 (9.1%); p=NSMyalgia: 6/173 (3.4%) vs. 6/176 (3.4%); p=NSLeukopenia: 5/173 (2.8%) vs. 5/176 (2.8%); p=NS | Roche |

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| **Author, YearCountryStudy NameQuality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **AgeSexRace** | **GenotypeSeverity of Liver DiseaseProportion Treatment-Naïve** |
| Ferenci, 200849AustriaA 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 3Overall Quality: Fair | A: Pegylated interferon alpha-2a 180 μg/week/24 weeksB: Pegylated interferon alpha-2a 180 μg/week/24 weeks | A: Ribavirin 800 mg/day/24 weeksB: Ribavirin 400 mg/day/24 weeks | None | Treatment-naive adultAged 18 to 65 yearsChronic hepatitis CHCV genotype 2 or 3 infectionQuantifiable 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/ LPlatelet count 100,000/ LSerum 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 timeCo infected with hepatitis B virus or human immunodeficiency virusDecompensated liver disease or chronic liver disease attributableto another causeCoronary heart diseaseDiabetes mellitus requiring insulin therapyAutoimmune disordersAny other unstable chronic medical conditionSevere psychiatric disease, especially depressionHistory 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. BAge (Mean): 37 vs. 36 years Female: 40% vs. 38%Race: NR | A vs. BGenotype 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. 5.7Cirrhosis: NRMinimal or no fibrosis: NR100% Treatment naïve |

| **Author, YearCountryStudy NameQuality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Ferenci, 200849AustriaContinued | Followup visits at 24 weeks after completion of treatment | A vs. BETR: NRSVR: 97/141(68.8%) vs. 90/141(63.8%) | NR | A vs. BSVR:Genotype 2 - 14/18(77.8%) vs. 12/16(63.2%); p=NSGenotype 3 - 83/12(67.5%) vs. 78/122(63.9%); p=NS | NR | A vs. BOverall withdrawals: 13/141 (9%) vs. 22/141 (16%) p=NSWithdrawals due to adverse events: NRDeaths: NRSevere Adverse Events: NRAdverse events: Pruritus: 48/141 (34%) vs. 50/141 (35%); p=NSPsychiatric events (mostly depression): 49/141 (35%) vs. 56/141 (40%); p=NSHemoglobin <8.5 g/dL: 2/141 (1.4%) vs. 1/141 (0.7%); p=NSNeutrophils <1000/mm3: 73/141 (52%) vs. 71/141 (50%); p=NSPlatelets <50K/mm3: 6/141(4%) vs. 6/141 (4%); p=NS | Roche, Austria |

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| **Author, YearCountryStudy NameQuality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **AgeSexRace** | **GenotypeSeverity of Liver DiseaseProportion Treatment-Naïve** |
| Fried., 200850USAImproved Outcomes in Patients with Hepatitis C with Difficult-to-Treat Characteristics: Randomized Study of Higher Doses of Pegylated interferon ά-2a and RibavirinOverall Quality: Fair | A: Pegylated interferon alfa-2a 180 μg/week/48 weeks B: Pegylated interferon alfa-2a 180 μg/week/48 weeksC: Pegylated interferon alfa-2a 270 μg/week/48 weeksD: Pegylated interferon alfa-2a 270 μg/week/48 weeks | A: Ribavirin 1200 mg/day/48 weeksB: Ribavirin 1600 mg/day/48 weeksC: Ribavirin 1200 mg/day/48 weeksD: Ribavirin 1600 mg/day/48 weeks  | None | Treatment-naïveAge 18 years or olderWeighing 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 testElevated serum alanine aminotransferase level within the previous 6 monthsCompensated liver diseaseLiver biopsy specimen consistent with chronic hepatitis C obtained within the previous 24 months | Infection with an HCV genotype other than 1Previous treatment with interferon-based therapy, ribavirin, or any investigational drug for chronic hepatitis CHistory or other evidence of liver disease not associated with chronic hepatitis CNeutrophil count 1.5 x 10^9 cells/LPlatelet count 90 109 cells/LHemoglobin level 12 g/dL in women and 13 g/dL in men Increased risk of anemia or for whom anemia would be medically problematicSerum creatinine level more than 1.5 times the upper limit of normalCo infection with hepatitis B virus or human immunodeficiencyvirusOther serious chronic diseaseHistory 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. DAge (Mean): 47.1 vs. 49.6 vs. 47.1 vs. 48.5 yearsFemale: 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. DGenotype 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. 5.2100% Treatment naïve |

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| **Author, YearCountryStudy NameQuality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
| Fried, 200850USAContinued | Followup visits at 24 weeks after completion of treatment | A vs. B vs. C vs. DETR: 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. DOverall 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: NRSerious 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, YearCountryStudy NameQuality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **AgeSexRace** | **GenotypeSeverity of Liver DiseaseProportion Treatment-Naïve** |
| Helbling, 200651SwitzerlandHCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon α-2a and ribavirinOverall Quality: Fair | A: Pegylated interferon alpha-2a 180 μg/week/48 weeksB: 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 weeksB: (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 yearsBiopsy proved (within <12 months) chronic hepatitis C with advanced fibrosis/cirrhosis (Ishakstage F4–F6<7 Child–Pugh pointsNo previous antiviral treatmentElevated alanine aminotransferase (ALT; on >2 occasions within >6 months)Serum HCV RNA positiveHemoglobin >11 g/dLNeutrophil count >1500/lLPlatelet count >75 000/lLSerum creatinine <1.5 times upper limit of normalNormal fasting glucose (or <8 μmol/L provided HbA1c <8.5%)Hbs-antigen negativeantinuclear antibodies <1:160Normal thyroid stimulating hormoneNormal alpha-fetoproteinFocal lesions ruled out by ultrasound (within 1 month of study entry) | Concomitant liver diseaseOngoing substance abuse including alcohol (>80 g/day)Hepatocellular carcinomaClinically relevant disorders of other organs/systemsPregnancy or lactationRefusal to practice effective contraception during treatment/followup Immunomodulatory treatment within 6 months or treatment withany investigational drug within 30 days of study entry | NR/126/ 126/124 | A vs. BAge - Median: 47 vs. 47 yearsFemale: 30% vs. 40%Race: NR | A vs. BGenotype 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, YearCountryStudy NameQuality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Helbling, 200651SwitzerlandContinued | Followup visits at 24 weeks post-treatment | A vs. BETR: NRSVR: 33/64(52%) vs. 23/60(38%), p=0.153 | NR | A vs. BETR: NRSVR: 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. BDiscontinuation: 15/64 (23%) vs. 16/60 (27%); p=NSDiscontinuation (due to AE): 6/64(9%) vs. 9/60(15%); p=NSOverall withdrawals: 18/64(28%) vs. 23/60(38%); p=NSDeaths: 0/64(0%) vs. 2/60(3%); p=NSSevere Adverse Events: 9/64(14%) vs. 11/60(18%); p=NSAdverse events:Psychiatric - 1/64(2%) vs. 4/60(7%); p=NSNeurologic - 3/64 (5%) vs. 1/60(2%); p=NSInfectious - 1/64(2%) vs. 2/60(3%); p=NSNeoplastic - 2/64 (3%) vs. 1/60(2%); p=NSSkin - 0/64(0%) vs. 1/60(2%); p=NSEndocrine and Metabolism - 0/64(0%) vs. 1/60(2%); p=NSEye - 1/64(2%) vs. 0/60(0%); p=NSGastrointestinal - 0/64(0%) vs. 1/60(2%); p=NSCardiovascular - 1/64(2%) vs. 0/60(0%); p=NS | NR |

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| **Author, YearCountryStudy NameQuality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **AgeSexRace** | **GenotypeSeverity of Liver DiseaseProportion Treatment-Naïve** |
| Jacobson, 200752USA (236 practice sites nation-wide)Pegylated interferon alfa-2b and Weight-Based or Flat-Dose Ribavirin in Chronic Hepatitis C Patients: A Randomized TrialJacobson, 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 1Overall Quality: Fair | A: Pegylated interferon alfa-2b 1.5 µg/kg 1x/week/24 - 48 weeks depending on genotypeB: 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 genotypeB: Ribavirin 800-1400 mg/day for 24-48 weeks depending on genotype<65kg - Ribavirin 800 mg/week/48 weeks65-85 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 patients18 to 70 years oldBody weight less than 125 kgTreatment-naive adult patients with HCV RNA levels detectable by (PCR)/branched DNA assayCompensated liver diseaseLiver biopsy showing HCV infection within 36 months prior to screeningElevated ALT at least once during the 6 months prior to screeningAlpha-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/ 4913Paper 2: 4913/ 387/ 387/ 387(sub population from Jacobson , 2007a) | A vs. BAge - Mean: - 45.8 vs. 45.8 yearsFemale - 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. BGenotype 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 naivePaper 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: NR100% Treatment naïve |

| **Author, YearCountryStudy NameQuality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Jacobson, 200752USA (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. BETR: 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. B65-85 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. BGenotype1: 337/1305 (29%) vs. 447/1313 (34%); p=0.005Genotype 2/3: 462/777 (60%) vs. 479/775 (62%); p=0.252Genotype 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. BDiscontinuation: 354/2444(14.5%) vs. 369/2469(14.9%); p=NSOverall withdrawals: 913/2444(37.3%) vs. 895/2469(36.2%); p=NSDeath: 5/2444(<1%) vs. 9/2469(<1%); p=NSSerious Adverse Event: 279/2444(11.4%) vs. 287/2469(11.6%); p=NSAdverse events:Cardiovascular – 136/2444(5.6%) vs.162/2469(6.6%); p=NSPsychiatric - 1685/2444(68.9%) vs. 1667/2469(67.5%); p=NSAnemia - 473/2444(19.4%) vs. 721/2469(29.2%); p<0.001Paper 2 (African Americans):Discontinuation: 85/202(42%) vs. 68/165(41%); p=NSOverall withdrawals: 35/202(17% ) vs. 30/165(18%); p=NSDeaths: NRSevere Adverse Events: NRAdverse 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=0.04RBV dose-reduction - 53/202(26%) vs. 69/185(37%);p=0.02Nadir 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=NSNadir 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, YearCountryStudy NameQuality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **AgeSexRace** | **GenotypeSeverity of Liver DiseaseProportion Treatment-Naïve** |
| Kawaoka, 200954JapanDose comparison study of pegylated interferon-α-2b plus ribavirin in naïve Japanese patients with hepatitis C virus genotype 2: A randomized clinical trialOverall Quality: Fair | A: Pegylated interferon alpha-2a 1.0 μg/kg/week/24 weeksB: 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 weeksB: 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 yearsTreatment naïve Genotype 2 | Patients treated with Shosaiko-to, a Japanese herbal medicine considered to improveliver function Patients with autoimmune hepatitisPatients with a history of hypersensitivity to Pegylated Interferon-alpha-2a or other interferonsHistory of hypersensitivity to biologicalproducts, such as vaccinesDecompensated liver cirrhosis (LC) Hepatocellular carcinoma (HCC) or malignant tumors in other tissuesHistory of severe psychosis, such as being severely depressed and/or suicidal Women who were pregnant or lactating orwho were suspected of being pregnantPatients judged by the investigator not to be appropriate for inclusion | NR/ 55/ 53/ 53 | A vs. BAge - Median: 57 vs. 55 yearsFemale: 65% vs. 44%Race: NR (study conducted in Japan)  | A vs. BGenotype 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: NoneMinimal or no fibrosis: 55% vs. 48%100% Treatment naive |

| **Author, YearCountryStudy NameQuality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Kawaoka, 200954JapanContinued | 24 weeks following treatment completion | A vs. BETR: 23/26(88.5%) vs. 25/27(92.6%), p=0.13SVR: 10/26(38.5%) vs. 20/27(74.1%), p=0.013 | NR | NR | NR | A vs. BOverall withdrawals/drop-out: 2/26(7.2%) vs. 2/27(7.6%); p=NSDiscontinuation (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=NSDeaths: NRSevere Adverse Events: NRAdverse events (leading to dose-reduction):Thrombocytopenia - 1/26(4%) vs. 0/27(0%); p=NSFatigue - 1/26(4%) vs. 3/27(11%); p=NSNeutropenia - 0/26(0%) vs. 1/27(4%); p=NSAnemia - 15/26 (57.7%) vs. 10/27 (37%); p=NSReduced Ribavirin - 21/26 (80.7%) vs. 22/27(81.5%); p=NS | NR |

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| **Author, YearCountryStudy NameQuality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **AgeSexRace** | **GenotypeSeverity of Liver DiseaseProportion Treatment-Naïve** |
| Krawitt, 200655USA (New York/New England)A Study of Low Dose Pegylated interferon Alpha-2b with Ribavirin for the Initial Treatment of Chronic Hepatitis COverall 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 olderDetectable serum hepatitis C virus (HCV) RNATreatment naiveLiver 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 locationsChronic hepatitis alone (F0)Chronic hepatitis with fibrosis, including bridging fibrosis (F1–F3)Chronic hepatitis with cirrhosis (F4)  | Positive serum hepatitis B surface antigenAny chronic liver disease other than chronic hepatitis CHemoglobinopathiesEvidence 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 disordersActive substance dependency within 6 months of screening for entry into the studyMethadone maintenance (unless a program of continual testing was in use)History of organ transplantationParticipation in any other clinical trial or use of another investigational drug within 30 days of entry | NR/NR/ 314/301 | A vs. BAge:> 50 years - 18% vs. 19%Female - 38% vs. 36%Race: Non White - 4.6% vs. 3.1% | A vs. BGenotype 1 - 109/152(71.7%) vs. 119/162(73.5%)Genotype 2/3 - 43/152(28.3%) vs. 43/162(26.5%)HistologyFibrosis - 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 |

| **Author, YearCountryStudy NameQuality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Krawitt, 200655USA (New York/New England)Continued | Followup visits at 24 weeks Post-treatment | A vs. BETR: NRSVR: 50/152(33%) vs. 73/162(45%), p=0.02 | A vs. BETR: NRSVR: 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= 0.29Male: 29/94 (31%) vs. 44/110 (40%); p=0.14Female - 21/58(36%) vs. 29/52(56%), p=0.06Race:Caucasian - 50/145 (34%) vs. 70/157 (45%), p= 0.08African-American - 0/6 (0%) vs. 3/4 (75%), p= 0.03Hispanic/Other - 0/1 (0%) vs. 0/1 (0%), p= 1.00Weight: < 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. BETR: NRSVR: HCV Genotype: Genotype 1 - 26/109 (24%) vs. 45/119 (38%), p= 0.03Genotype 2/3 - 24/43 (56%) vs. 28/43 (65%), p= 0.51Baseline 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= 1.00Histology:No fibrosis or cirrhosis: 17/46 (37%) vs. 29/53 (55%); p=0.11Fibrosis - 27/80 (34%) vs. 39/92 (42%), p= 0.27Cirrhosis - 6/26 (23%) vs. 5/17 (29%), p= 0.73 | NR | A vs. BTotal Discontinuation: 9/147(6%) vs. 28/154(18%); p=0.0015Discontinuation due to AE: 5/147(3%) vs. 14/154(9%); p=0.04Overall withdrawals: NRDeaths: NRSevere Adverse Events: NR | Integrated Therapeutics Group (Schering-Plough) |

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| **Author, YearCountryStudy NameQuality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **AgeSexRace** | **GenotypeSeverity of Liver DiseaseProportion Treatment-Naïve** |
| Manns, 200156US & UKPeginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trialOverall Quality: Fair | A: Pegylated interferon alfa-2b 1·5 g/kg/4 weeks followed byPegylated 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 weeks75 kg > 1000 mg75 kg < 1200 mg B: (weight-based) Ribavirin 1000–1200 mg/day/48 weeks75 kg > 1000 mg75 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 yearsFemale: 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%HistologyMean (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% |

| **Author, YearCountryStudy NameQuality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Manns, 200156US & UKContinued | 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. 34/505Serious adverse events: NR Deaths: NRAdverse Events:Anemia: 9/511 vs. 12/514 vs. 13/505Neutropenia: 18/511 vs. 10/514 vs. 8/505Asthenia 18/511 vs. 16/514 vs. 18/505Fatigue 64/511 vs. 62/514 vs. 60/505Fever 46/511 vs. 44/514 vs. 33/505Headache 62/511 vs. 58/514 vs. 58/505Rigors 48/511 vs. 45/514 vs. 41/505Weight decrease 29/511 vs. 17/514 vs. 20/505Dizziness 21/511 vs. 21/514 vs. 17/505Arthralgia 34/511 vs. 34/514 vs. 28/505Musculoskeletal pain 21/511 vs. 17/514 vs. 19/505Myalgia 56/511 vs. 48/514 vs. 50/505Anorexia 32/511 vs. 29/514 vs. 27/505Diarrhea 22/511 vs. 16/514 vs. 17/505Nausea 43/511 vs. 36/514 vs. 33/505Vomiting 14/511 vs. 14/514 vs. 12/505Concentration impairment 17/511 vs. 16/514 vs. 21/505Depression 31/511 vs. 29/514 vs. 34/505Insomnia 40/511 vs. 40/514 vs. 41/505Irritability 35/511 vs. 34/514 vs. 34/505Coughing 17/511 vs. 15/514 vs. 13/505Dyspnea 26/511 vs. 23/514 vs. 24/505Alopecia 36/511 vs. 29/514 vs. 32/505Pruritus 29/511 vs. 26/514 vs. 28/505Rash 24/511 vs. 22/514 vs. 23/505Dry skin 24/511 vs. 18/514 vs. 23/505Injection-site inflammation 25/511 vs. 27/514 vs. 18/505Injection-site reaction 58/511 vs. 59/514 vs. 36/505 | Schering PloughResearch 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, YearCountryStudy NameQuality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **AgeSexRace** | **GenotypeSeverity of Liver DiseaseProportion Treatment-Naïve** |
| Meyer-Wyss, 200657SwitzerlandComparison 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 fibrosisOverall Quality: Poor | A: Pegylated-interferon alpha-2b 1.0 μg/kg/week/24-48 depending on genotypeB: Pegylated-interferon alpha-2b 1.5 μg/kg/week/24-48 depending on genotype | A: Ribavirin 800mg/day/24-48 depending on genotypeB: Ribavirin 800mg/day/24-48 depending on genotype | None | Treatment-naive patientsAged 18–65 yearsBiopsy-proven chronic hepatitis C within <12 monthsUp 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 womenPositive human immunodeficiency virus (HIV)statusLiver disease other than chronic hepatitis CElevated levels of fasting blood glucoseAbnormal values of thyroid stimulating hormoneHemophilia or HemoglobinopathyAny known pre-existing medical condition that could interfere with the patient’s participation and completion of the study including: History of severe psychiatric disordersCentral nervous system trauma/active seizure disordersSignificant cardiovascularPulmonary, or retinal disordersClinically manifested goutSubstance abuseChronic systemic administration of steroids/other immunosuppressantsImmunologically mediated disease. | NR/NR/ 227/219 | A vs. BAge - Median: 39 vs. 42 yearsFemale: 43% vs. 28%Race: NR | A vs. BGenotype 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: NoneMinimal of no fibrosis: NR100% Treatment naive |

| **Author, YearCountryStudy NameQuality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Meyer-Wyss , 200657SwitzerlandContinued | Followup visits at 4 and 24 weeks post-treatment | A vs. BETR: NRSVR: 61/113(53%) vs. 56/106(53%), p= ns | NR | A vs. BETR: 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=0.01Deaths: 0/115(0%) vs. 1/112(0%); p=NSLife-threatening Adverse Events: 4/115(3%) vs. 9/112(9%); p=NSSevere Adverse Events: 62/115(54%) vs. 59/112(53%); p=NSWithdrawals due to AE: 22/115 (19%) vs. 34/112 (30%); p=0.05Adverse events (only body systems listed with at least 10% of patients reporting):Thrombocytopenia: 1/115(1%) vs. 1/112(1%); p=NSLeukopenia: 9/115(8%) vs. 5/112(4%); p=NSNeutropenia: 20/115(17%) vs. 18/112(16%); p=NSHemolytic anemia: 3/115(3%) vs. 3/112(3%); p=NSBlood and lymphatic system disorders - 44/115(38.3%)vs. 41/112 (36.6%); p=NSGeneral disorders and administration site conditions - 112/115(97.4%) vs. 108/112(96.4%); p=NSGastrointestinal disorders - 81/115(70.4%)vs. 84/112(75.0%); p=NSMetabolism and nutrition disorders -16/115(13.9%) vs. 29/112(25.9%); p=0.02Musculoskeletal and connective tissue disorders - 27/115(23.5%) vs. 33/112(29.5%); p=NSNervous system disorders - 70/115(60.9%) vs. 80/112(71.4%); p=NSPsychiatric disorders - 71/115(61.7%) vs. 76/112(67.9%); p=NSRespiratory, thoracic and mediastinal disorders 18/115(15.7%) vs. 24/112(21.4%); p=NSSkin and subcutaneous disorders -83/115(72.2%) vs. 76/112(67.9%); p=NS | Essex Chemie AG, Lucerne |

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| **Author, YearCountryStudy NameQuality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **AgeSexRace** | **GenotypeSeverity of Liver DiseaseProportion Treatment-Naïve** |
| Mimidis, 200658GreeceHepatitis 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 dataOverall Quality: Poor | A. Pegylated interferon alfa-2b 3.0 mcg/kg weekly for 12 weeks followed by 1.5 mcg/kg weekly for 36 weeksB. 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-naïveHCV RNA detected in serumLiver biopsy consistent with chronic hepatitis within 6 months before enrollmentElevated ALT at entry and at least once in 6 months before screening | HBVHIV coinfectionHemochromatosisAlpha-1 anti-trypsin deficiencyWilson's diseaseAutoimmune hepatitisAlcohol drug or obesity induced liver diseaseSubstance abuseAny known pre-existing condition that could interfere with patient's participationCreatinine >1.5 mg/dL Neutrophils <1000/mL3Platelets <50K/mL3Hemoglobin <11 g/dL | NR/NR/ 188/120 | A vs. BAge mean: NRSex: 36% vs. 38%non White: NR | A vs. Bgenotype 1/4: 46% vs. 52%Treatment-naïve: allFibrosis: NRCirrhosis: NRHCV RNA> 800k IU/mL: NR |

| **Author, YearCountryStudy NameQuality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Mimidis, 200658GreeceContinued | Week 72 | A vs. BETR: NRSVR: 38/89 (42.7%) vs. 47/87 (54%) | NR | A vs. BGenotype 1: 9/35 (25.7%) vs. 18/40 (45%); p=NSGenotype 2/3: 23/48 (47.9%) vs. 25/42 (59.5%); p=NSGenotype 4: 6/6 (100%) vs. 4/5 (80%); p=NS | NA | NR | NR |

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| **Author, YearCountryStudy NameQuality** | **Interferon Regimen** | **Ribavirin Regimen** | **Protease Inhibitor Regimen** | **Eligibility** | **Exclusion** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **AgeSexRace** | **GenotypeSeverity of Liver DiseaseProportion Treatment-Naïve** |
| Reddy, 201059International, 14 countriesInduction pegylated interferon alfa-2a and high dose ribavirin do not increase SVR in heavy patients with HCV genotype 1 and high viral loadsOverall Quality: Fair | A. Pegylated interferon alpha-2a 360 mcg weekly for 12 weeks then 180 mcg weekly for 36 weeksB. Pegylated interferon alpha-2a 360 mcg/weekly for 12 weeks then 180 mcg weekly for 36 weeksC. Pegylated interferon alpha-2a 180 mcg weekly for 48 weeksD. Pegylated interferon alpha-2a 180 mcg weekly for 48 weeks | A. 1400 - 1600 mg/day for 48 weeks depending on weightB. 1200 mg/day for 48 weeksC. 1400 - 1600 mg/day for 48 weeks depending on weightD. 1200 mg/day for 48 weeks | NA | Treatment-naïveAged 18 years or olderWeight > 85 kgHCV genotype 1 infectionHCV RNA > 400k IU/mLLiver biopsy in past 24 months consistent with chronic hepatitis C | coinfection with HBV, HAV, or HIVChronic liver disease of other originCurrent or past history of chronic systemic disease including severe psychiatric diseaseIncreased baseline risk of anemiaNeutrophils <1500/mL3Platelets <90K/mL3Hemoglobin<12 g/dL in men or <13 g/dL in womenCreatinine >1.5 times upper limit of normalPregnant or breastfeeding women and male partners | NR/NR/ 1175/1145 | A vs. B vs. C vs. DAge mean: 46 vs. 46 vs. 45 vs. 46Female: 19% vs. 24% vs. 22% vs. 19%non White: 14% vs. 13% vs. 19% vs. 13% | A vs. B vs. C vs. Dgenotype 1: allTreatment-naïve: allBridging fibrosis/cirrhosis: 12% vs. 8% vs. 10% vs. 12%HCV RNA >800k IU/mL: 86% vs. 83% vs. 84% vs. 82% |

| **Author, YearCountryStudy NameQuality** | **Duration of Followup** | **Outcome** | **Subgroup Analyses** | **Subgroup Analyses** | **Histologic Response** | **Adverse Events** | **Funding Source** |
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| Reddy, 201059International, 14 countriesContinued | Week 72 | A vs. B vs. C vs. DETR: NRSVR: 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. DOverall 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=NSWithdrawals 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=NSSerious 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=NSDeaths: 2/383 (<1%) vs. 2/382 (<1%) vs. 3/189 (1%) vs. 1/191 (<1%); A vs. C p=NS; B vs. D p=NSPyrexia: 205/383 (54%) vs. 176/382 (46%) vs. 78/189 (41%) vs. 83/191 (43%); A vs. C p=NS; B vs. D p=NSFatigue: 182/383 (48%) vs. 185/382 (48%) vs. 102/189 (54%) vs. 66/191 (35%); A vs. C p=NS; B vs. D p=NSHeadache: 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=0.002Chills: 132/383 (34%) vs. 122/382 (32%) vs. 55/189 (29%) vs. 42/191 (22%); A vs. C p=NS; B vs. D p=0.001Myalgia: 113/383 (30%) vs. 98/382 (26%) vs. 45/189 (24%) vs. 46/191 (24%); A vs. C p=NS; B vs. D p=NSArthralgia: 89/383 (23%) vs. 88/382 (23%) vs. 49/189 (26%) vs. 50/191 (26%); A vs. C p=NS; B vs. D p=NSDepression: 58/383 (15%) vs. 72/382 (19%) vs. 36/189 (19%) vs. 32/191 (17%); A vs. C p=NS; B vs. D p=NSHemoglobin <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, 201059International, 14 countriesContinued |  |  |  |  |  | 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=NSPlatelets <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, 200960AustraliaImpact of high-dose Pegylated interferon alfa-2a on virologic response rates in patients with hepatitis C genotype 1: a randomized controlled trialOverall 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 weeksB. 1000-1200 mg/day for 48 weeks | NA | Treatment naïveAges 18 -75 yearsHCV genotype 1 infectionHCV RNA >600 IU/mLElevated ALTCompensated 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 | HBVHIV coinfectionHistory of decompensated liver diseaseEvidence of hepatocellular carcinomaLiver disease of other originTherapy with systemic antiviral, antineoplastic, or immunomodulatory agents within 6 monthsPregnancy or breast feeding and male partner of women Neutrophils <1500/mL3Hemoglobin <12 g/dL in women and <13 g/dL in menCreatinine >1.5 times the upper limit of normalActive severe psychiatric diseaseAny severe chronic or uncontrolled diseaseCurrent or recent drug or alcohol abuseCirrhosis | NR/NR/ 896/871 | A vs. BAge mean: 44 vs. 43Female: 31% vs. 35%non White: 18% vs. 17% | A vs. Bgenotype 1: allTreatment-naïve: allFibrosis stage 3 or 4: 14% vs. 16%HCV RNA > 800K: 70% vs. 67% |

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| Roberts, 200960 AustraliaContinued | 24 weeks after end of treatment (week 72) | A vs. BETR: 70% vs. 66%; p=0.18SVR: (230/433) 53% vs. (219/438) 50%; p=0.29 | A vs. BWhite: 183/355 (52%) vs. 167/365 (46%); p=NSAsian: 40/61 (66%) vs. 40/55 (73%); p=NSOther: 7/17 (41%) vs. 12/18 (67%); p=NSMale: 149/298 (50%) vs. 134/285 (47%); p=NSFemale: 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=NSWeight <85 kg: 167/294 (57%) vs. 156/297 (53%); p=NSWeight >85 kg: 63/139 (45%) vs. 63/141 (45%); p=NS | A vs. BHCV RNA <800K: 81/125 (65%) vs. 84/138 (61%); p=NSHCV RNA >800K: 147/302 (49%) vs. 132/293 (45%); p=NSFibrosis METAVIR stage 3 or 4: 17/60 (28%) vs. 16/67 (24%); p=NSFibrosis METAVIR stage 0,1,or 2: 148/256 (58%) vs. 134/242 (55%); p=NS | NR | A vs. BOverall withdrawals: 113/433 (26%) vs. 136/438 (31%); p=NSWithdrawals due to adverse events: 44/433 (10%) vs. 36/438 (8%); p=NSDeaths: NRSerious adverse events: 46/433 (11%) vs. 45/438 (10%); p=NSHeadache: 227/433 (52%) vs. 208/438 (47%); p=NSInfluenza like illness: 180/443 (42%) vs. 183/438 (42%); p=NSNausea: 179/433 (41%) vs. 169/438 (39%); p=NSFatigue: 159/433 (37%) vs. 174/438 (40%); p=NSMyalgia: 114/433 (26%) vs. 97/438 (22%); p=NSRash: 110/433 (25%) vs. 116/438 (26%); p=NSDepression: 84/433 (19%) vs. 85/438 (19%); p=NSArthralgia: 82/433 (19%) vs. 76/438 (17%); p=NSPyrexia: 66/433 (15%) vs. 47/438 (11%); p=NSChills: 64/433 (15%) vs. 34/438 (8%); p<0.001Neutropenia: 76/433 (21%) vs. 55/438 (13%); p=0.05Thrombocytopenia: 17 (4%) vs. 6 (1%); p=0.02Anemia: 5 (1%) vs. 3 (1%); p=NS | Roche |

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| Sood, 200861IndiaComparison 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 ExperienceOverall Quality: Fair | A: Pegylated-interferon alpha-2b 1.0 μg/kg/week/24 weeksB: Pegylated-interferon alpha-2B 1.5 μg/kg/week/24 weeks | A: Ribavirin 10-12 mg.kg/day/24 weeksB: Ribavirin 10-12 mg.kg/day/24 weeks | None | Aged between 16–70-years-oldHCV-RNA positive with genotype 3Treatment naïveALT >1.2 x Upper limit of Normal (ULN) at screening and for at least the previous 6 monthsLiver biopsy–proven chronic HCV within 6 months prior to inclusion | Chronic HCV patients with genotypes other than Genotype 3Total leukocyte count < 3000 per cubic millimeterPlatelet count < 70 000 per cubic millimeter,Hemoglobin level lower than 10 g per deciliterco infection with hepatitis B virus or human immunodeficiencyvirus, Alcohol intake exceeding 20 g/dayPresence of drug abuse, psychiatric illness, or thyroid dysfunctionPregnancy and lactation Decompensated liver disease Evidence of liver disease due to other etiology such as autoimmune or drug-inducedhepatitisSerious 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. BAge - Mean: 43 vs. 37 yearsFemale: 12% vs. 22%Race: NR | A vs. BGenotype 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: NR100% Treatment naïve |

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| Sood, 200861IndiaContinued | Followup visits at 24 weeks post-treatment | A vs. BETR: 72/76(94.7%) vs. 24/27(88.9%), p=0.375SVR: 60/76(78.9%) vs. 25/27(926%), p=0.145 | NR | NR | NR | A vs. BOverall withdrawals: 1/76 (1.3%) vs. 2/27 (7.4%); p=NSWithdrawals (due to AE): 0/76 vs. 1/27 (4%); p=NSDeaths: NRSevere Adverse Events: NRAdverse events: Influenza-like symptoms - 20/27(74.0 %%) vs. 44/76(57.9%); p=NSMalaise or fatigue -10/27(37.0%) vs. 22/76(29.0%); p=NSNausea or vomiting - 5/27(18.5%) vs. 11/76(14.5%) p=NSHeadache - . 4/27 (14.8%) vs. 8/76(10.5%); p=NSAbdominal discomfort - 4/27(14.8%) vs. 8/76 (10.5%); p=NSDiarrhea - . 4/27(14.8%) vs. 9 /76(11.8%); p=NSGrade III or IV laboratory abnormalities Neutrophils - 3/27(11.1%) vs. 1/76(1.3%); p=0.02Platelets - 4/27(14.8%) vs. 2/76(2.6%); p=0.02 | NR |