



HEPATITIS WEB STUDY  HEPATITIS C ONLINE

## Ribavirin (*Copegus, Rebetol, Ribasphere*)

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## Interferon alfa-2b +/- Ribavirin for Chronic HCV Study Conclusions

**Conclusions:** “In patients with chronic hepatitis C, initial therapy with interferon and ribavirin was more effective than treatment with interferon alone.”

Treatment Naïve, Chronic HCV

## Peginterferon alfa-2a +/- Ribavirin for Chronic HCV

Fried MW, et. al. N Engl J Med. 2002;347:975-82.

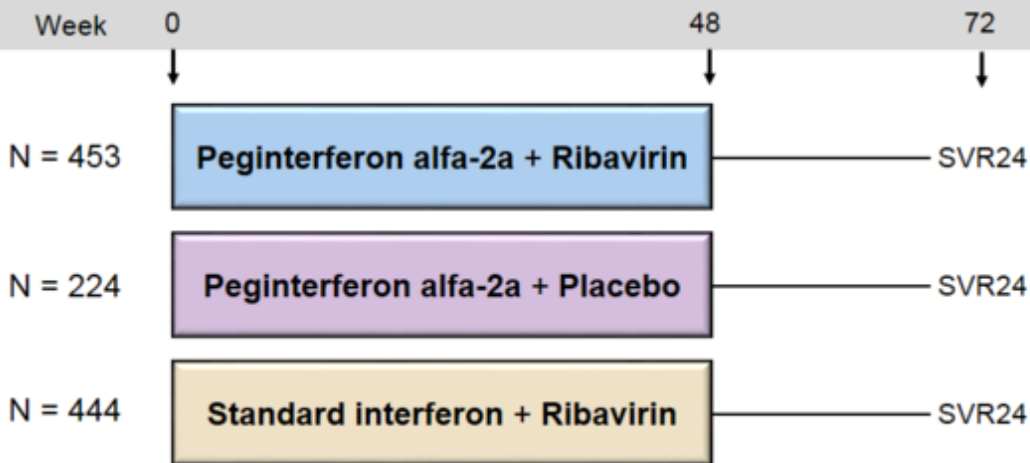
# Peginterferon alfa-2a +/- Ribavirin for Chronic HCV Study Design

- **Study**
  - Open-label randomized controlled trial
- **Subjects**
  - N = 1149 with chronic hepatitis C randomized
  - Treatment naïve; 62% genotype 1
  - Serum ALT above upper limit of normal x prior 6 months
- **Regimens (48 Week Treatment)**
  - Peginterferon alfa-2a 180 µg 1x/week + Ribavirin 1000-1200 mg/day
  - Peginterferon alfa-2a 180 µg 1x/week + Placebo
  - Interferon alfa-2b 3 million U 3x/week + Ribavirin 1000-1200 mg/day
- **Primary Endpoint**
  - Undetectable serum HCV RNA 24 weeks after stopping treatment

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\*Ribavirin dosing: <75 kg = 1000 mg/day; ≥75 kg = 1200 mg/day

# Peginterferon alfa-2a +/- Ribavirin for Chronic HCV Study Design



## Drug Dosing

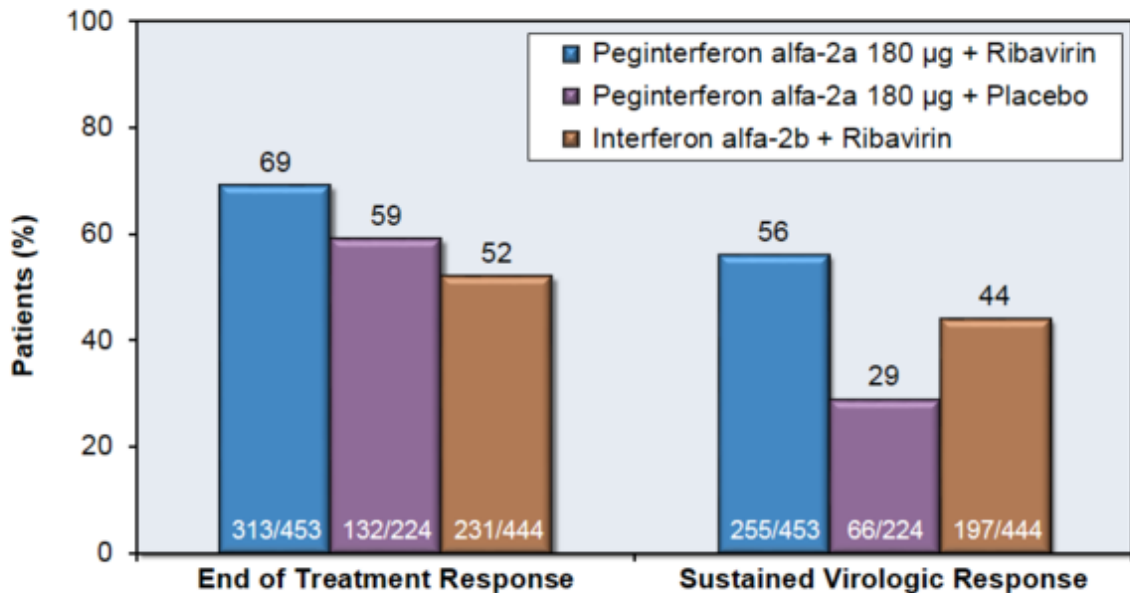
Peginterferon alfa-2a 180 µg 1x/week

Weight-based Ribavirin (divided bid): 1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg

Interferon alfa-2b 3 million U 3x/week

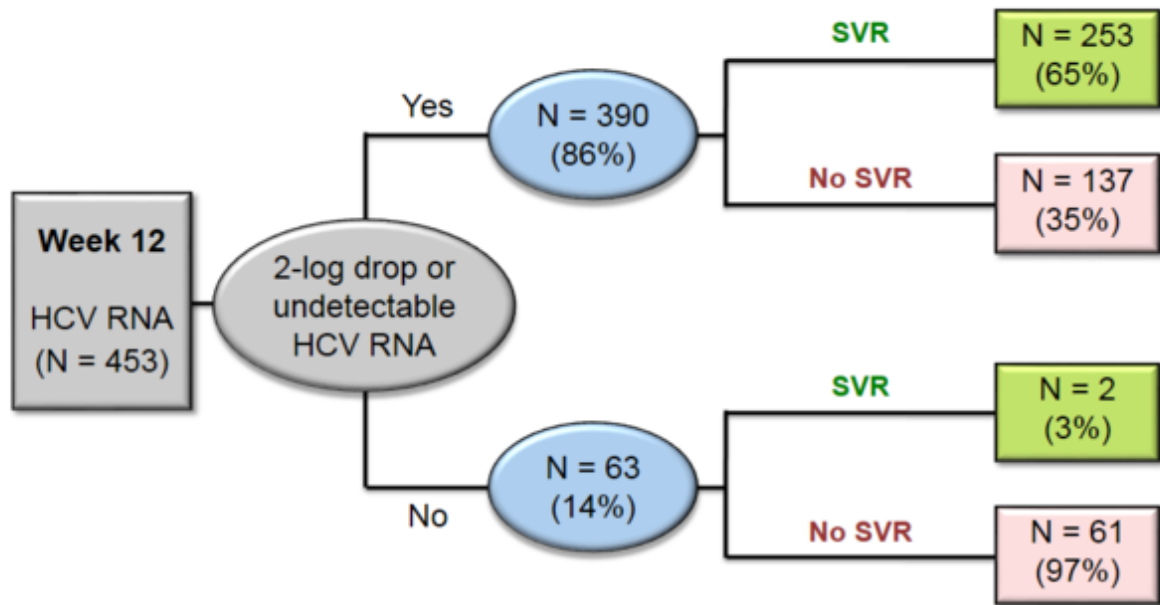
# Peginterferon alfa-2a + Ribavirin for Chronic HCV Results

## Response after 48 Weeks of Treatment



# Peginterferon alfa-2a + Ribavirin for Chronic HCV

## Predictive Value of Early Virologic Response



## Peginterferon (with and without Ribavirin) versus Interferon and Ribavirin

**Conclusions:** “In patients with chronic hepatitis C, once-weekly peginterferon alfa-2a plus ribavirin was tolerated as well as interferon alfa-2b plus ribavirin and produced significant improvements in the rate of sustained virologic response, as compared with interferon alfa-2b plus ribavirin or peginterferon alfa-2a alone.”



Treatment Naïve, Chronic HCV

## Duration and Dose Finding Peginterferon alfa-2a + Ribavirin

Randomized study of low-dose versus weight based ribavirin and 24 versus 48 weeks of therapy

Hadziyannis SJ, et. al. Ann Intern Med. 2004;140:346-55.

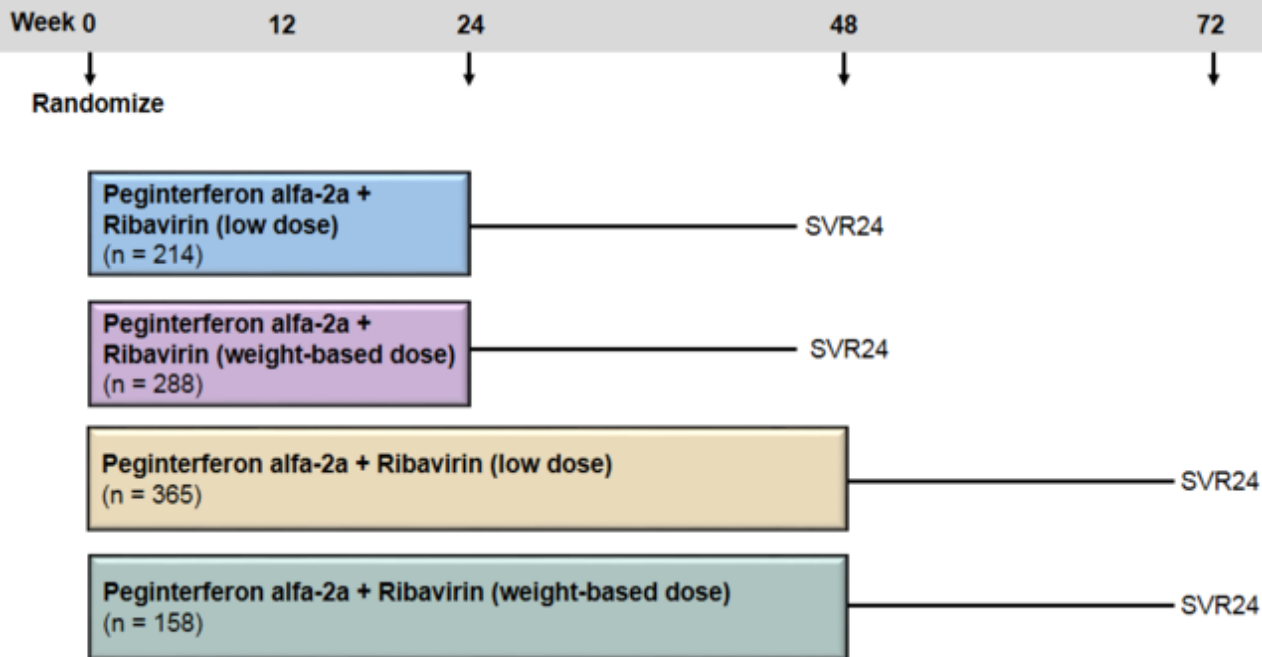
# Peginterferon alfa-2a + Ribavirin for Chronic HCV

## Treatment Duration and Ribavirin Dose

- **Study**
  - Randomized, double-blind trial
- **Subjects**
  - N = 1311 with chronic hepatitis C (1284 treated)
  - Treatment naïve adult patients; 58% genotype 1
  - Serum ALT above upper limit of normal x prior 6 months
- **Regimens**
  - Peginterferon alfa-2a: 180 µg/wk + Ribavirin: 800 mg/day x 24 wks
  - Peginterferon alfa-2a: 180 µg/wk + \*Ribavirin: 1000-1200 mg/day x 24 wks
  - Peginterferon alfa-2a: 180 µg/wk + Ribavirin: 800 mg/d x 48 weeks
  - Peginterferon alfa-2a: 180 µg/wk + \*Ribavirin: 1000-1200 mg/day x 48 wks
- **Primary Endpoint**
  - Undetectable serum HCV RNA at end of treatment (ETR)
  - Undetectable serum HCV RNA 24 wks after cessation of treatment (SV)

\*Ribavirin dose: 1000 mg/day for Wt <75 kg, 1200 mg/day for Wt ≥75 kg

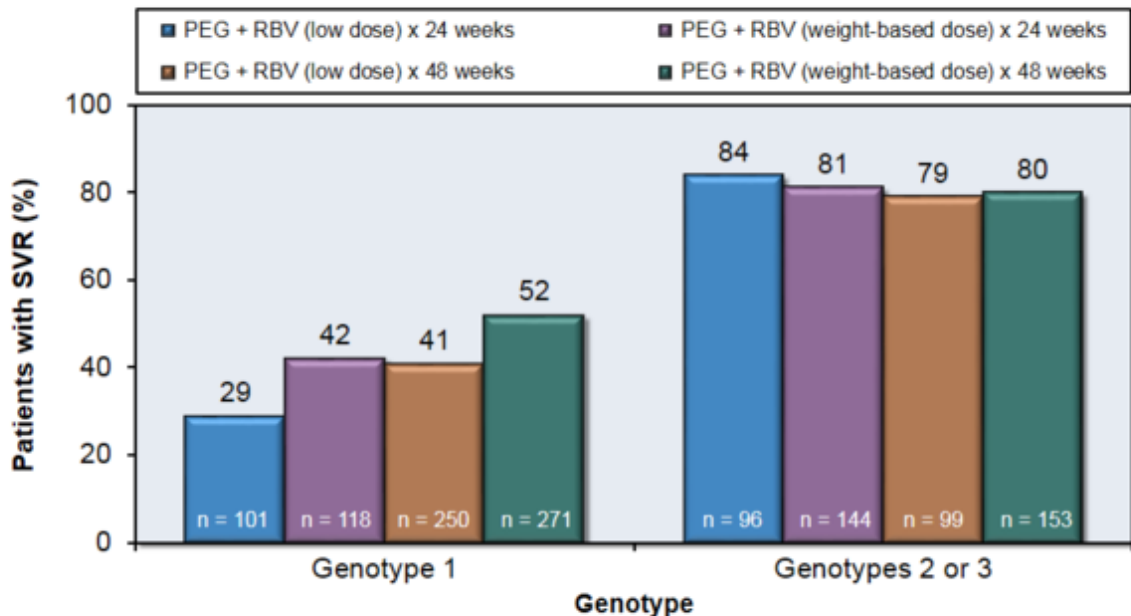
# Peginterferon alfa-2a + Ribavirin for Chronic HCV Treatment Duration and Ribavirin Dose



RIBAVIRIN (*COPEGUS, REBETOL, RIBASPHERE*)  
Background

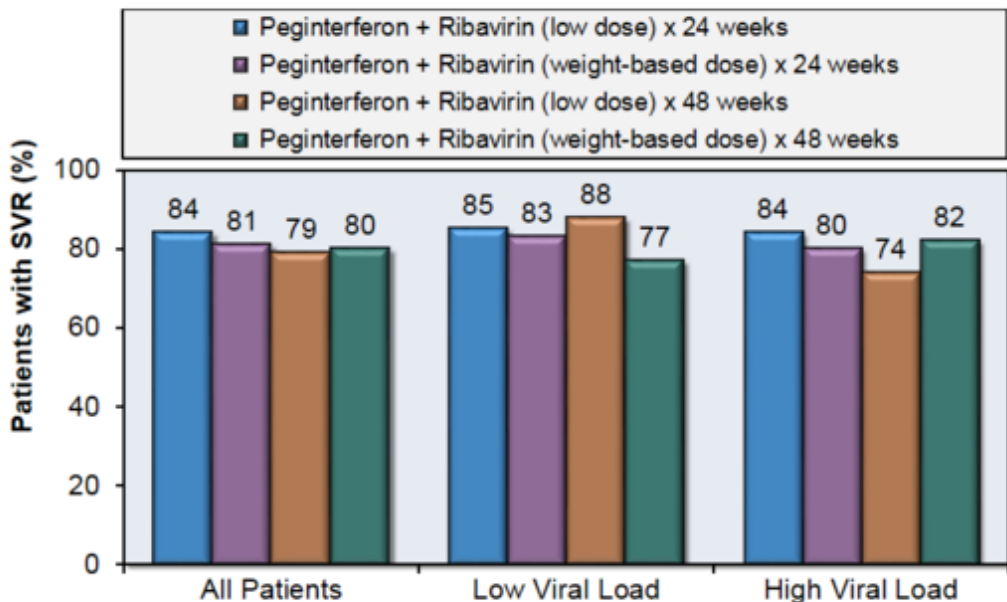
# Peginterferon alfa-2a + Ribavirin for Chronic HCV Treatment Duration and Ribavirin Dose

## SVR24 Rates, by Regimen



# Peginterferon alfa-2a + Ribavirin for Chronic HCV Treatment Duration and Ribavirin Dose

Rates of SVR with Different Peginterferon + Ribavirin Regimens



## Peginterferon alfa-2a + Ribavirin for Chronic HCV Treatment Duration and Ribavirin Dose

**Conclusion:** “Treatment with peginterferon-alpha2a and ribavirin may be individualized by genotype. Patients with HCV genotype 1 require treatment for 48 weeks and a standard dose of ribavirin; those with HCV genotypes 2 or 3 seem to be adequately treated with a low dose of ribavirin for 24 weeks.”

Treatment Naïve, Chronic HCV

## WINR Study Flat versus Weight-Based Ribavirin Dosing

Jacobson IM, et. al. Hepatology. 2007;46:971-81.

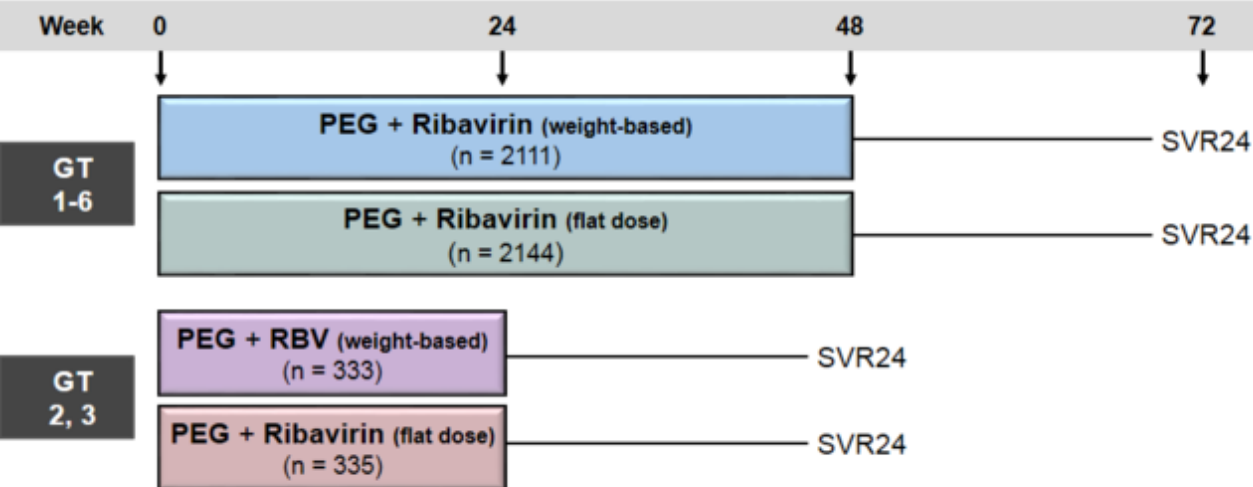


# Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose) WIN-R Study: Design

- **Study**
  - Prospective, randomized, open-label trial
- **Subjects**
  - N = 5027 with chronic hepatitis C (4913 analyzed)
  - Treatment naïve adult patients (Age 18-70)
- **Treatment Regimens**
  - Peginterferon alfa-2b: 1.5 µg/kg/wk + Wt-based\* Ribavirin: 800-1400 mg/d
  - Peginterferon alfa-2b: 1.5 µg/kg/wk + Flat-dose Ribavirin: 800 mg/d
- **Treatment Duration**
  - Genotypes 1,4,5,6: duration of 48 weeks
  - Genotypes 2,3: duration of 24 or 48 weeks
- **Primary Endpoint**
  - Undetectable serum HCV RNA at end of treatment (ETR)
  - Undetectable serum HCV RNA 24 weeks after cessation of treatment (SVR)

\*Weight-based ribavirin dosing: < 65 kg: 800 mg/d; 65-85 kg: 1000 mg/d; >85-105 kg: 1200 mg/d; >105 kg: 1400 mg/d

# Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose) WIN-R Study: Design



## Drug Dosing

Peginterferon alfa-2b: 180 µg once weekly

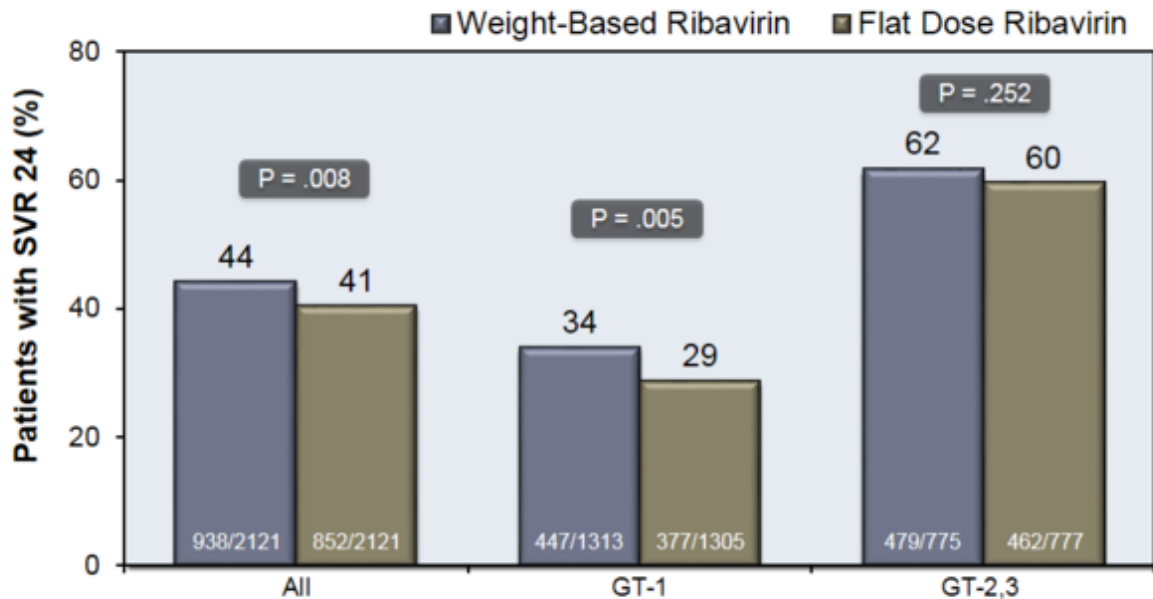
Weight-based Ribavirin (in 2 divided doses):

- 800 mg/d if < 65 kg; 1000 mg/d if 65-85 kg; 1200 mg/d if >85-105 kg; 1400 mg/d if >105 kg

Flat-dose Ribavirin (in 2 divided doses): 800 mg/day

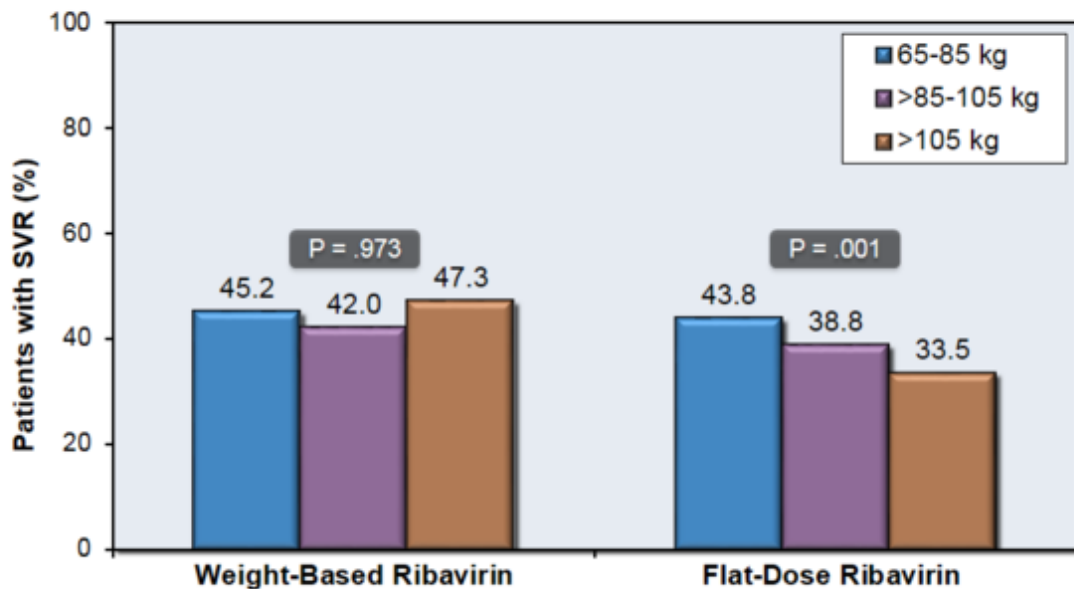
# Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose) WIN-R Study: Results

## SVR 24, by Genotype and Treatment Regimen



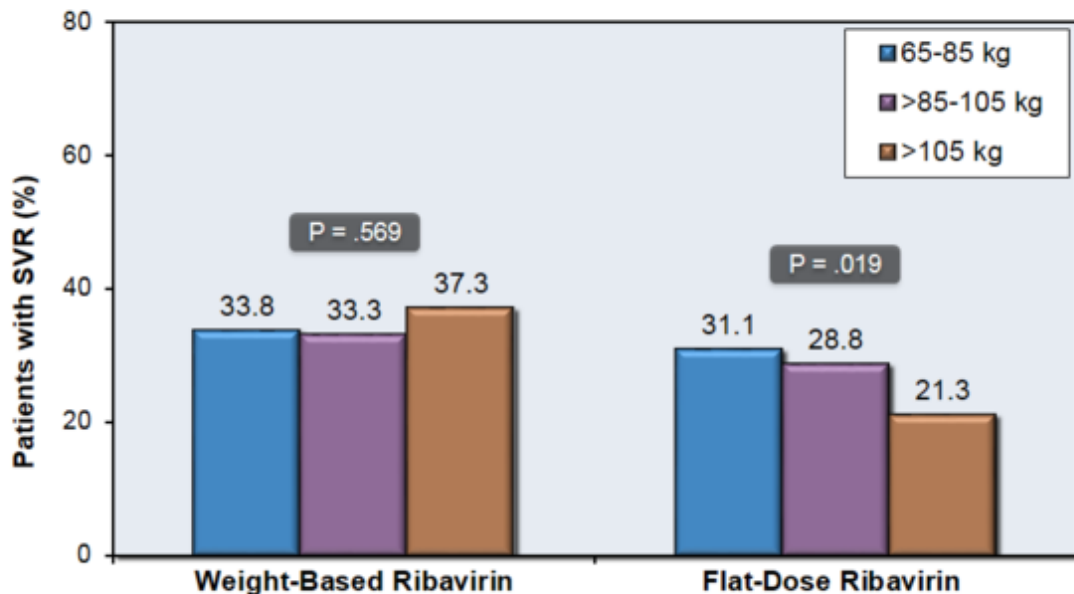
# Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose) WIN-R Study: Results

All Treated: SVR24 by Weight Distribution



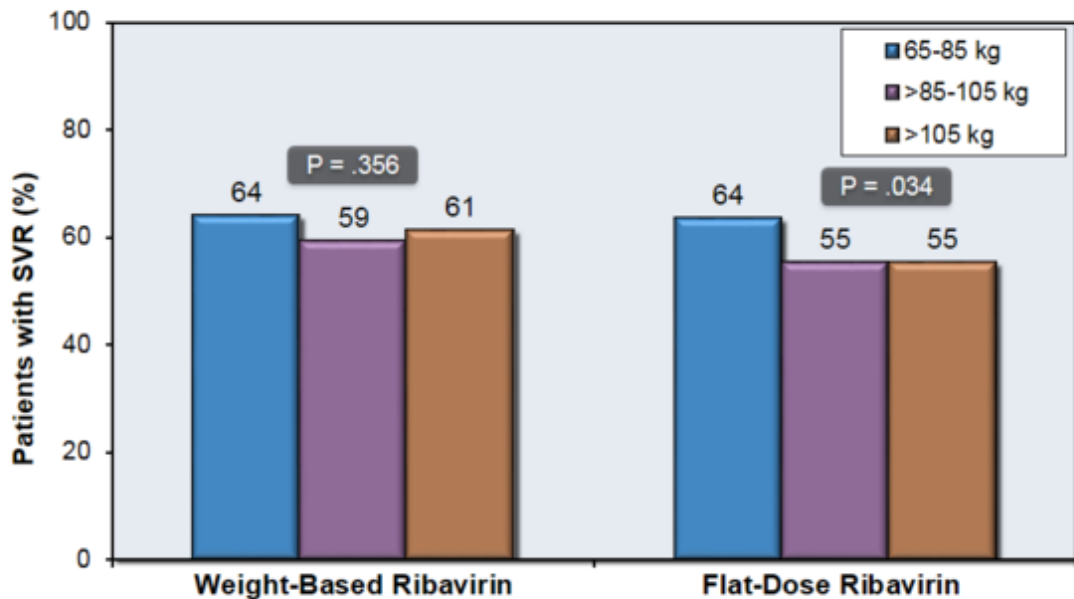
# Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose) WIN-R Study: Results

## Genotype 1: SVR24 by Weight Distribution

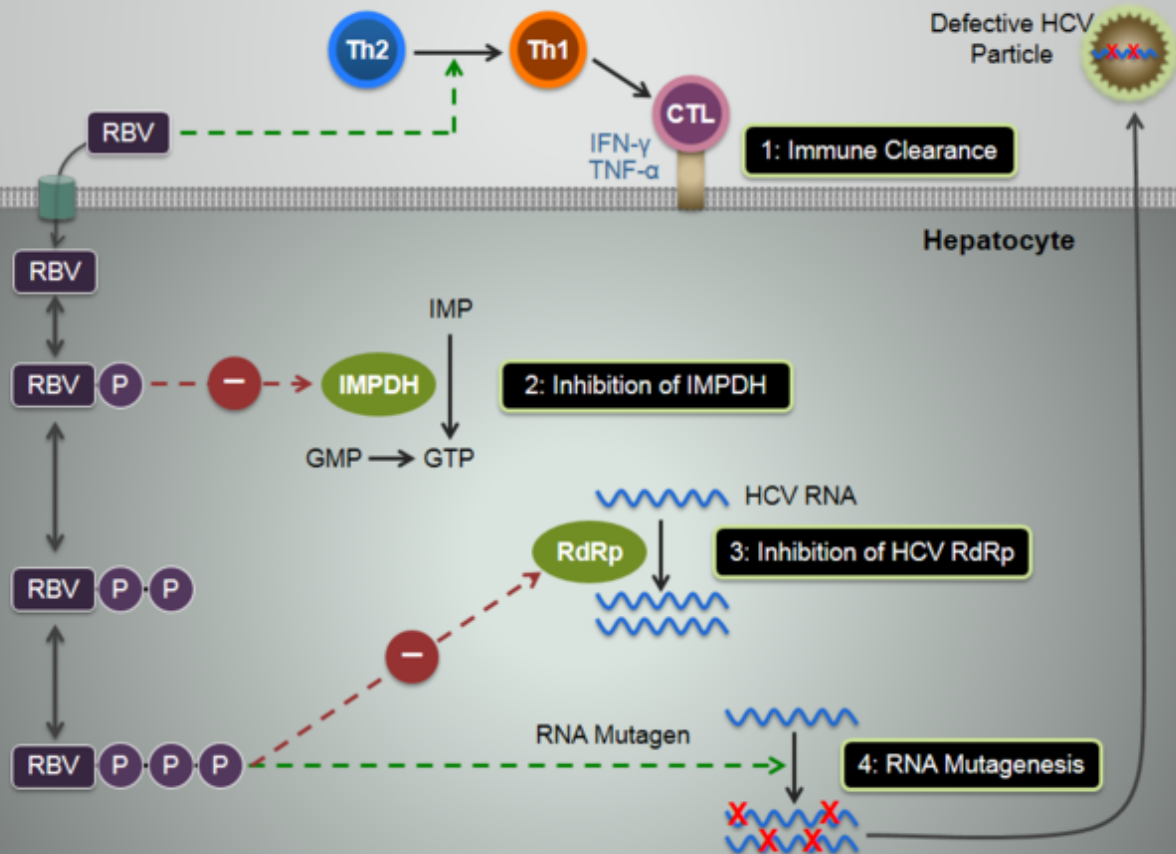


# Peginterferon alfa-2b & Weight-based or Flat-dose Ribavirin WIN-R Study: Results

## Genotypes 2,3: SVR24 by Weight Distribution

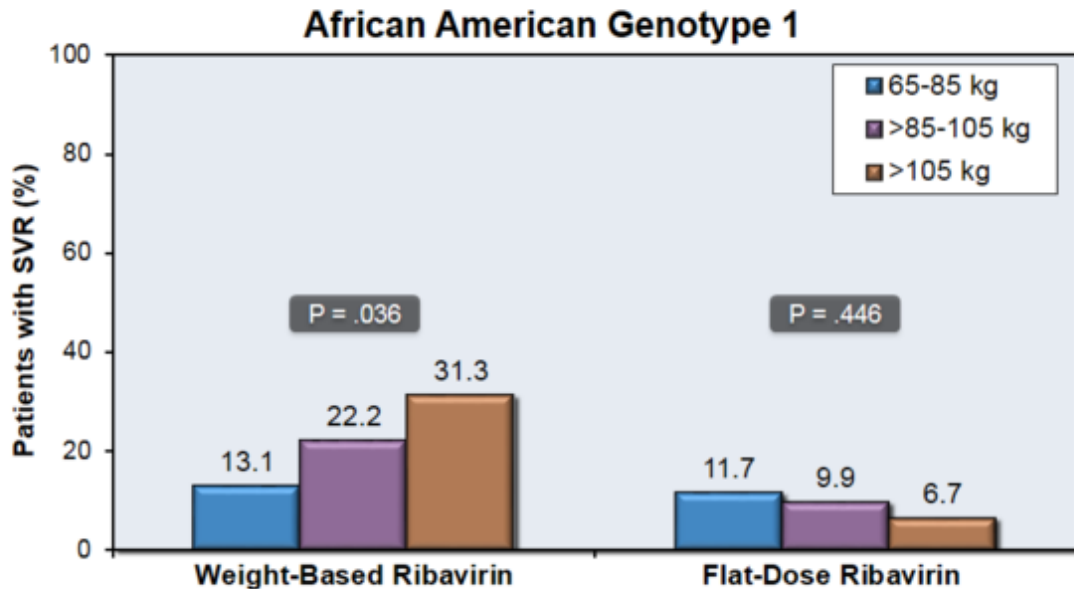


# Ribavirin: Mechanism of Action



# Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose) WIN-R Study: Results

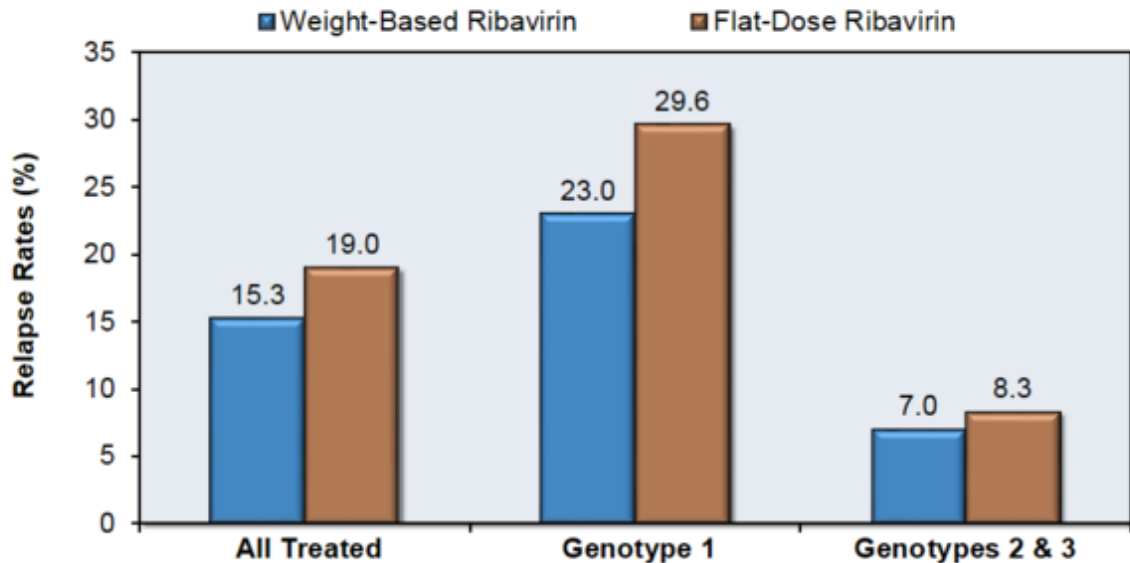
## Sustained Virologic Response (SVR) by Weight Distribution





# Peginterferon alfa-2b & Weight-based or Flat-dose Ribavirin WIN-R Study: Results

Relapse Rates among Patients who Achieved End-of-Treatment Responses



## Peginterferon alfa-2b & Weight-based or Flat-dose Ribavirin WIN-R Study: Conclusions

**Conclusion:** “Peginterferon alfa-2b plus weight-based ribavirin is more effective than flat-dose ribavirin, particularly in genotype 1 patients, providing equivalent efficacy across all weight groups. Ribavirin 1400 mg/day is appropriate for patients 105 to 125 kg. For genotype 2/3 patients, 24 weeks of treatment with flat-dose ribavirin is adequate; no evidence of additional benefit of extending treatment to 48 weeks was demonstrated.”

This slide deck is from the University of Washington's *Hepatitis C Online* and *Hepatitis Web Study* projects.

Hepatitis C Online

[www.hepatitisc.uw.edu](http://www.hepatitisc.uw.edu)

Hepatitis Web Study

<http://depts.washington.edu/hepstudy/>

Funded by a grant from the Centers for Disease Control and Prevention.

# Ribavirin (*Copegus, Rebetol, Ribasphere*)

- **Mechanism:** purine nucleoside analog
- **Approval Status:**
  - First approved by FDA in 1998
  - Multiple preparations subsequently FDA approved
- **Indications**
  - In combination with other agents for all HCV genotypes
- **Dosing** (brand dependent):
  - Fixed dose (800 mg PO per day in two divided doses)
  - Weight based (1000-1200 mg per day in two divided doses)
  - Weight based (800-1400 mg per day in two divided doses)
- **Drug Interactions**
  - Use of ribavirin and didanosine can cause life-threatening toxicity
  - Use of ribavirin and azathioprine can cause azathioprine-related toxicity
- **Adverse Effects (AE)**
  - Hemolytic anemia
  - Birth defects (pregnancy category X)

## Ribavirin: Key Studies

- Interferon alfa-2b +/- Ribavirin for 24 or 48 weeks
- Peginterferon alfa-2a +/- Ribavirin for Chronic HCV
- Duration and Dose Finding Peginterferon alfa-2a + Ribavirin
- Flat versus Weight-Based Ribavirin Dosing: WINR Study

Treatment Naïve, Chronic HCV

Interferon alfa-2b +/- Ribavirin for 24 or 48 weeks

McHutchison JG, et al. N Engl J Med. 1998;339:1485-92.

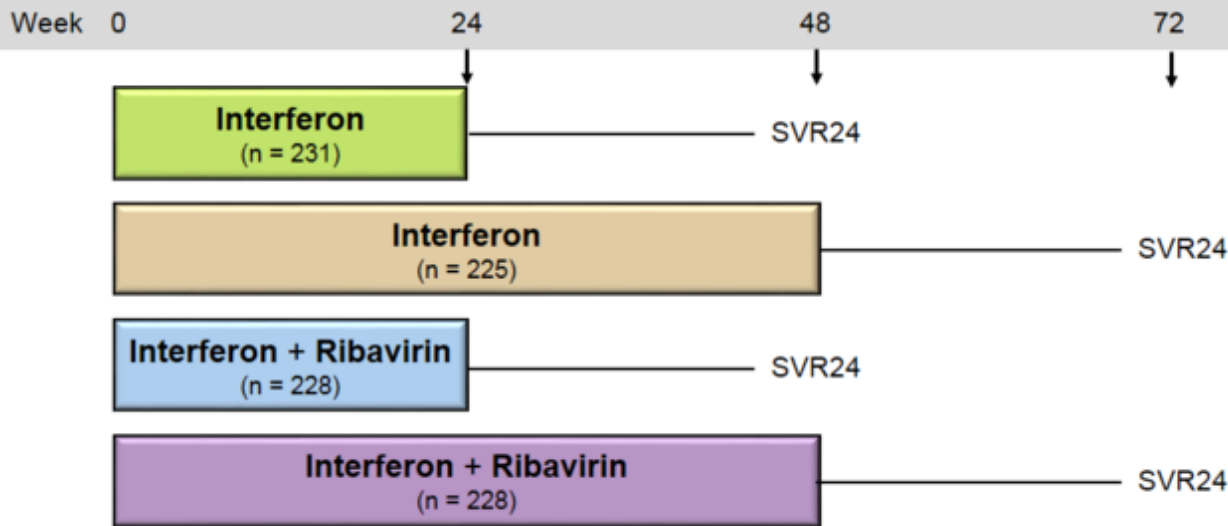
# Interferon alfa-2b +/- Ribavirin for Chronic HCV Study Outline

- **Study**
  - Randomized, double-blinded, placebo controlled, phase 3 trial
  - Conducted in 44 centers in United States
- **Subjects**
  - N = 912 with chronic hepatitis C
  - Treatment naïve; 72% genotype 1
- **Regimens**
  - Interferon alfa-2b + Placebo x 24 or 48 weeks
  - Interferon alfa-2b + Ribavirin (weight based) x 24 or 48 weeks
- **Primary Endpoint**
  - Undetectable serum HCV RNA 24 weeks after stopping treatment

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\*Ribavirin weight based dosing: <75 kg = 1000 mg/day; ≥75 kg = 1200 mg/day

# Interferon alfa-2b +/- Ribavirin for Chronic HCV Study Design



## Drug Dosing

Interferon alfa-2b 3 million U 3x/week

Weight-based Ribavirin (divided bid): 1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg



# Interferon alfa-2b +/- Ribavirin for Chronic HCV Study Results

## SVR 24, by Treatment Regimen

