Control arms, efficacy standards, design of future HCV trials

Filip Josephson

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Where are we now, interferon free?

- **GT1: 90%+ SVR in non-cirrhotic and compensated cirrhotic patients with SOF+potent DAA or NS5A+NS3/4A+non-nuc**
- **GT2: 90%+ SVR in most patient strata with SOF+RBV**
- **GT3: approx. 90% SVR with SOV+RBV in most patient strata; lower response in cirrhosis + other negative prognostic factors**
- **GT4: No larger studies of interferon free regimens**
- **Little data in decompensated liver disease**

Reflections on control arms in HCV trials

- **As SVR without treatment is 0, all SVR can be ascribed to the therapy given (no placebo response)**
- **Historical controls (e.g., NEUTRINO), placebo controls (e.g., POSITRON) and/or dosing regimen comparative studies (e.g. COSMOS) have informed decisions by European regulators**
- **Comparisons between interferon based and interferon free regimens are not requested**
- **Potential problem with no reference regimen control group:**

  study ”calibration” lacking - assessment of external validity is dependent on analysis of baseline demographic and disease factors

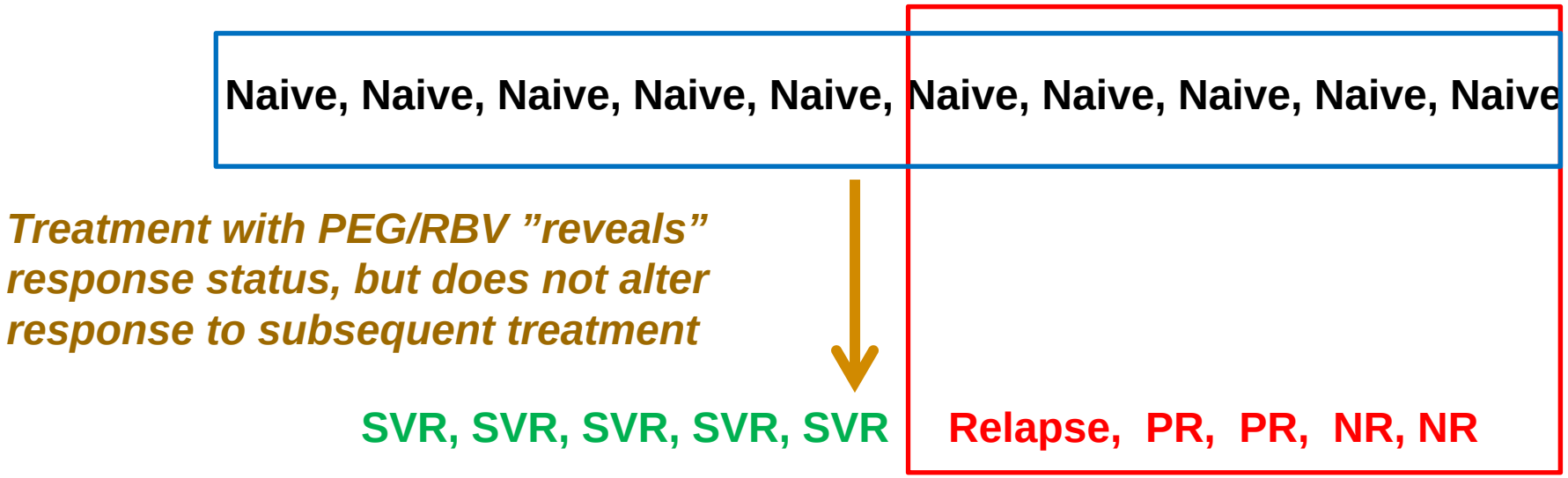
- **Potential problem with no reference regimen and no placebo control group:**

  Safety findings may be erroneously attributed to the investigational drug(s)

Considerations on phase III trials from draft updated CHMP guidance

- **Sponsors are generally encouraged to study the widest relevant range of patients in confirmatory phase III studies**
- **Which subpopulations in terms of, e.g., viral (sub)genotype, IL28B genotype, cirrhosis/non-cirrhosis and treatment experience are appropriate to study under the same protocol or under different protocols may vary from case to case.**

Treatment experienced (PEG/RBV) form a ”functional subgroup” of a treatment naive population



Those patients that do not reach SVR tend to have higher baseline HCV-RNA, more fibrosis, be IL28 non-C/C**.**

It is preferable that a development program is designed to allow extrapolation of, e.g., the optimal regimen duration between trial populations, and to facilitate the appropriate regimen selection in the clinic regardless of documentation of prior treatment response

Three principal scenarios are identified:

1. An entire new regimen (in most cases 2 or 3 new drugs) is investigated
2. A drug is investigated as an add-on to an approved combination
3. A drug is investigated as a substitute for one or more drugs in an approved combination

Further considerations on control arms

- **If there is no interferon-free regimen established for the particular genotype/study population, placebo controls or historical controls may suffice**
- **If there is an interferon-free regimen established for the particular genotype, this would generally be considered the appropriate reference treatment. Not using such a regimen as reference in clinical trials would need to be justified.**
- **If the investigational drug is used as an *add-on* to an approved regimen, or as a *substitute* for one or more of its components, that regimen should primarily be considered for comparison (superiority and non-inferiority design, respectively).**