Challenges in Phase II and III Studies for T2DM

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GSK Diabetes Portfolio

- Marketed Agents
  - Avandia®
  - Avandamet™
- Development Agents
  - Avandaryl
  - β3 agonist (‘353)
  - SGLT2 Inhibitor (‘682)
  - DPP-IV Inhibitor (‘093)
  - PPARpan (‘954)

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Phase 2 Goals and Considerations

- Efficacy in selected population with disease
  - Decision point for major investment
- Dose selection for pivotal trials
  - Dose range (no effect to maximum)

- Limited safety experience
  - Usually limited trial duration (<12 to 16 weeks)
- Time to complete

Efficacy for diabetes treatment

- Excellent surrogates (glucose, HbA1c)
  - Objective, continuous
- Simple to design study for primary efficacy
  - Make use of continuous property
  - Less information in categorical analyses
- More challenging to assess dose range
  - Therapeutic “window” impacts subject numbers

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Phase 2 Design Approaches

- Must incorporate ethical and treatment guideline considerations

- Question to be considered: to expose fewer subjects to greater degree of hyperglycemia or more subjects to lesser degree of hyperglycemia?

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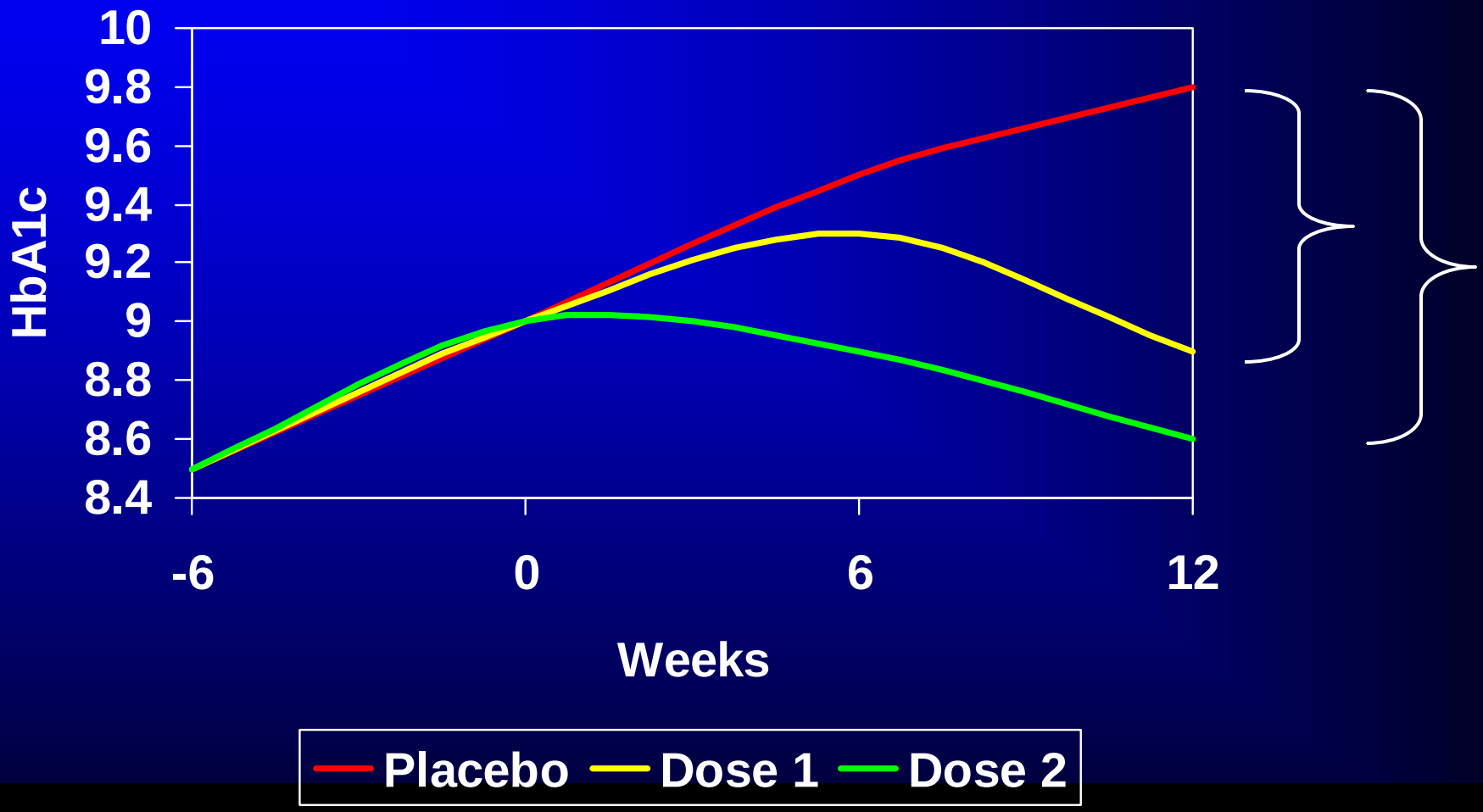
Washoff current therapy



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Considerations for washout studies

- Ethics of discontinuing effective therapy
- Duration of washout (differences between agents)
  - SUs with rapid washout
  - Metformin and TZD washout prolonged
- Removal of subjects due to worsening glycemia
  - What criteria? (HbA1c, FPG …..)
- No drug interactions
- “Clean” background for safety evaluation

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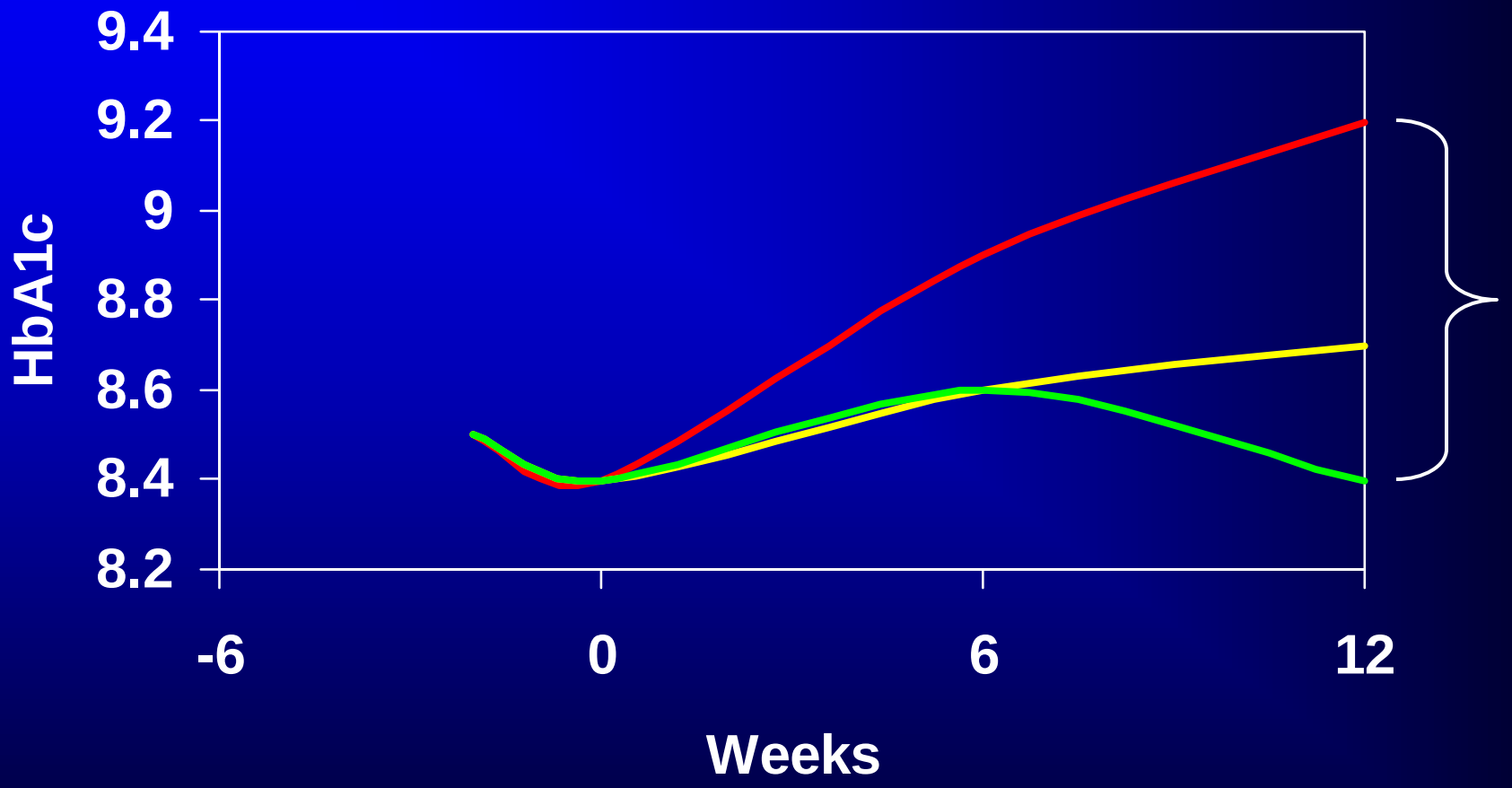
Withdraw therapy at randomization



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Considerations for withdrawal studies

- Ethics of discontinuing effective therapy
- Duration of study to see full effect
  - Washout of prior therapy
- Removal of subjects due to worsening glycemia
  - What criteria?
- No drug interactions
- “Clean” background for safety evaluation

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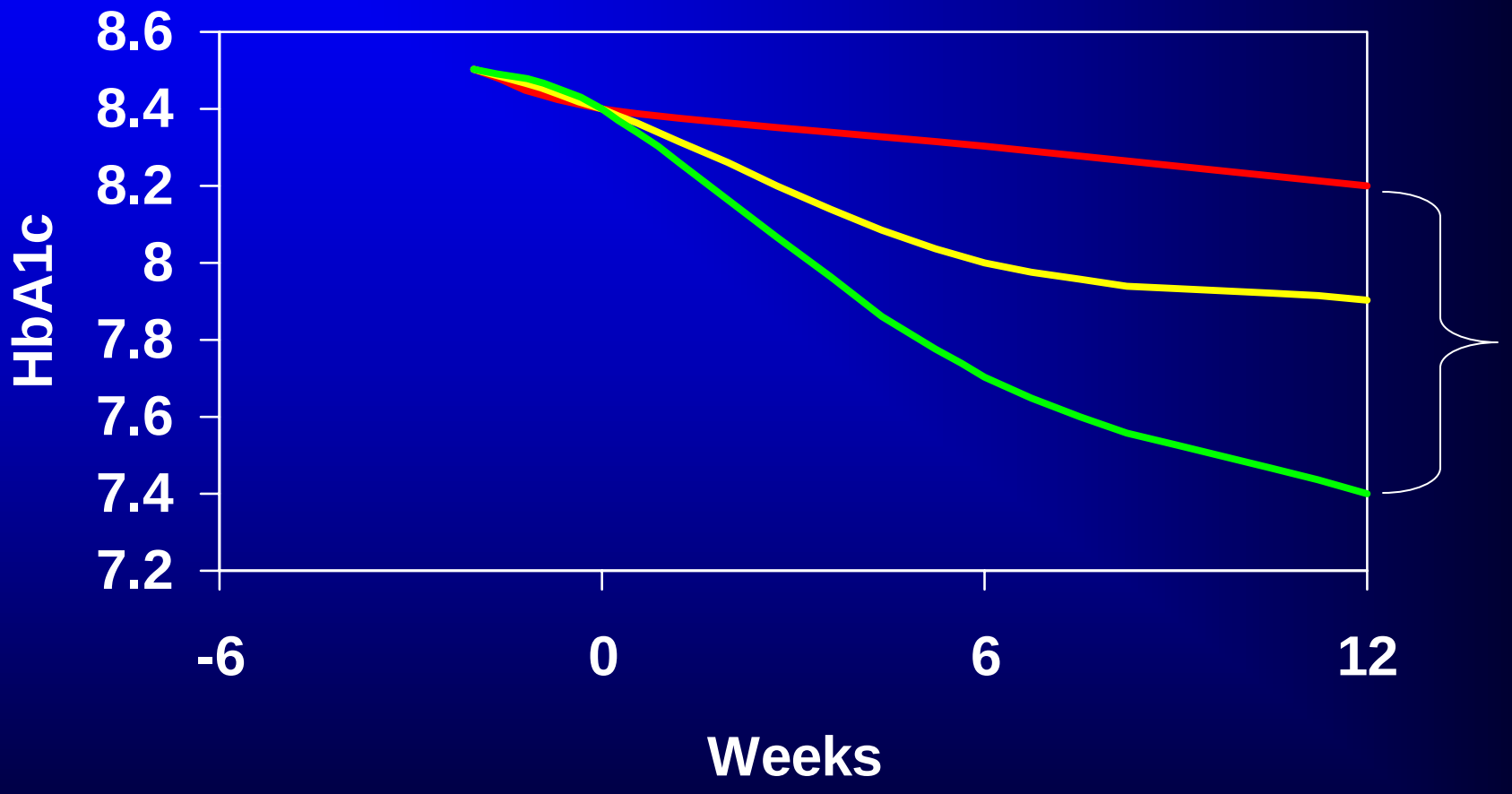
Add-on to existing therapy



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Considerations for add-on studies

- No discontinuation of effective therapy
- No worsening of glycemia (fewer withdrawals)
- Drug interactions must be considered
- “Mixed” background for safety evaluation

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Phase 2 Potential Pitfalls

- Recruiting
  - Drug naïve populations
  - Geographical difference in use of agents
- Differences in populations
  - Prior therapy
  - Starting HbA1c
- Dynamic range for endpoint
  - Entry criteria
  - Investigator bias (?)

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Phase 3 Challenges

- Safety evaluation (background event rates)
  - Unbalanced designs
  - Open label extensions
- Placebo treatment in longer duration trials
  - Removal of subjects for lack of effect

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Phase 3 Design Approaches

- Safety evaluation
  - Withdraw into auxiliary study if lack of efficacy
  - Allow “rescue” therapy if lack of efficacy
  - Parallel naturalistic trial with similar criteria
    - Mixed population for comparison
    - Choice of diabetes therapies to be used

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Monotherapy Study Considerations

- Population
  - Entry HbA1c (placebo?)
  - Prior therapies (monotherapy, combo therapy)
- Hyperglycemia withdrawal criteria
- Categorical efficacy analyses
  - Proportion of subjects withdrawn for hyperglycemia
  - Proportion of subjects with specified HbA1c

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Add-on Studies

- Population
  - Entry HbA1c (placebo?)
  - Prior therapy
    - Limit to specific agent (doses?)
      - Conventional add-on (second line – max dose)
      - First line (combination at less than maximal dose)
    - Change background at randomization
- Hyperglycemia withdrawal criteria
- Categorical efficacy analyses
  - Proportion of subjects withdrawn for hyperglycemia
  - Proportion of subjects with specified HbA1c

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Comparator Studies

- Population
  - Entry HbA1c
  - Prior therapies
- Dose management
  - Forced dose titration
  - Titration to glycemic target
- Hyperglycemia withdrawal criteria
- Categorical efficacy analyses
  - Proportion of subjects withdrawn for hyperglycemia
  - Proportion of subjects with specified HbA1c

Summary

- Design considerations in Phase II and Phase III are not consistent
  - Goal is to conduct trials that acknowledge ethical and current treatment guidelines
  - Need to evaluate dose response limits phase II flexibility
- Trials for newer agents will likely use different designs than currently approved agents..

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