BMS-955176: Characterization of a Second-Generation HIV-1 Maturation Inhibitor

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SUMMARY

Background: BMS-955176 is a second-generation HIV-1 maturation inhibitor (MI). A first-generation MI, bevirimat (BVM), showed efficacy in clinical trials but had limited utility because of high human serum binding and reduced activity associated with variable success of Gag polymorphisms. Assays designed to optimally target, specifically, potent, pan-oligotype, and human serum-resistant activity demonstrated that BMS-955176 exhibits high levels of activity toward a broad panel of HIV-1 isolates, including clinically relevant polymorphisms associated with resistance to BVM.

RESULTS

Development of a second-generation MI: insights from a first-generation MI, bevirimat (BVM).

The development of a first-generation MI, BVM, was terminated due to inadequate coverage of naturally occurring polymorphisms (SDMs) associated with reduced human serum binding. BMS-955176 was engineered to target human serum binding and activity against a diverse panel of HIV-1 isolates.

Effect of human serum on BMS-955176 potency.

A 5.4-fold serum shift in BMS-955176 EC50 was observed compared with 10% FBS serum shift for BVM.

BMS-955176 was ideal 3% (±4%) human serum protein.

Low serum protein/lipid binding increases free fraction of drug, which facilitates GI absorption.

BMS-955176 is an MI that binds specifically and reversibly to HIV-1 Gag, with a slow dissociation rate.

BMS-955176 blocks cleavage of CA precursor p26 to CA p24 in HIV-1 infected cells (Figure 3) and in Gag-p24 fusion proteins in cell-free systems (Figure 1). BMS-955176 inhibits Gag cleavage in HIV-1-infected cells and specific binding to Gag in virus-like particles (VLPs).

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BMS-955176 is active against a panel of ARV-resistant HIV-1 isolates.

BMS-955176 shows altered activity toward a panel of HIV-1 clinical isolates representing two major HIV-1 subtypes (A and B), and ARV-resistant viruses (with or without resistance to BVM).

Antiviral activity of BMS-955176 in a Phase Ia, randomized, multi-part trial (A4466002).

The present data support the further development of BMS-955176, and clinical data from the A4466002 study with the aim of applying the results of the present development strategy to identify a future clinical candidate.

METHODS

Viruses and cells

Recombinant soluble CD4 (sCD4) was used to mediate infection of TZM-bl-based reporter assays with virus particles. E. coli strains DH10B and TOP10 were used to amplify, purify, and sequence pBAGc plasmid DNA. Use structure-activity relationship (SAR) to develop a clinical candidate with antiviral activity toward a mature, infectious virus particles.

CONCLUSIONS

BMS-955176 demonstrates superior activity against a broad panel of ARV-resistant HIV-1 isolates and is a novel, high-activity MI for resistance to bevirimat (BVM).

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