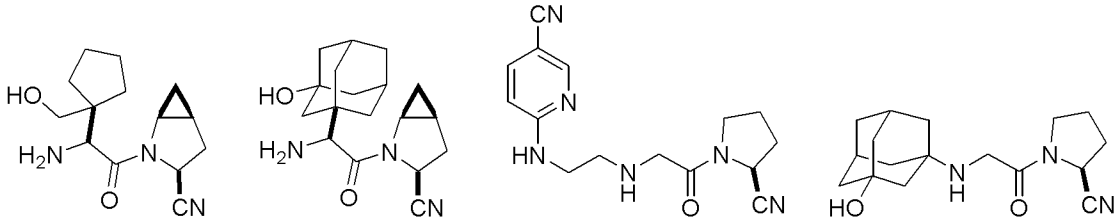
DP4-Chem-SE-103000.doc

Monthly Summary:

DP4 Inhibitors

The goal of the program is to discover small molecule inhibitors of dipeptidyl peptidase IV (DP4) for use in the treatment and prevention of diabetes. Inhibition of DP4 should prevent the degradation of GLP-1 and GIP, potentiating their actions in vivo. Solution stability studies on a series of 14 compounds has shown that at pH 7.2, 4,5-methanoproline containing DP4 inhibitors are significantly more stable than either 3,4-methanoproline- or non-cyclopropane-containing compounds, providing further support for this structural moiety beyond it's critical role in securing proprietary coverage for the chemotype. Hydroxyadamantyl analogue BMS-477118, synthesized as a result of PK and metabolism study results with the non-hydroxylated precursor, is the most potent reversible DP4 inhibitor known to date, with 6 hour ED50 of 0.5 umol/kg p.o. in the rat ex vivo plasma DP4 inhibition assay. This compares extremely favorably with the Phase II Novartis compound BMS-428245, which has > 100 umol/kg ED50 at this same 6 hour timepoint. Both BMS465980 and BMs-477118, the two most promising preclinical leads are currently undergoing extensive PD and PK characterization and toxicity profiling to enable ECN selection. As the more recent Novartis disclosure (BMS-471211) exhibits apparent slow-binding kinetics and subsequent improved ex vivo efficacy not observed with the Phase II compound BMS-428245, this compound will factor into benchmarking strategies as well.



BMS-465980 **BMS-477118** **Novartis DPP-728 BMS-428245** **Novartis BMS-471211**

Competitive Update: A patent application from Molteni L. E C. Dei Fratelli Alitta Societa' di Esercizio S.P.A. (WO 00/53171, Sept. 14, 2000) published, claiming the use of metformin in the preparation of pharmaceutical compositions capable of inhibiting DP4. In house in vitro assessment of metformin under our standard assay protocol showed no DP4 inhibition. Additional studies will be done to confirm this result.

Detailed Report:

DP4 Inhibitors

The goal of the program is to discover small molecule inhibitors of dipeptidyl peptidase IV (DP4) for use in the treatment and prevention of diabetes. Inhibition of DP4 should prevent the degradation of GLP-1 and GIP, potentiating their actions in vivo. The ECN target profile for a DP4 inhibitor emphasizes sufficient therapeutic window and/or duration of action to allow QD dosing in order to provide a competitive advantage versus the Novartis Phase II compound NVP-DPP-728, which will likely require multiple daily doses due to a reported 50 minute half-life in humans.

Solution stability studies conducted on a range of compounds from both proprietary an competitor chemotypes show encouraging SAR trends with this parameter (see Table 1). Relating the proline surrogate moiety structural features to pH 7.2 solution stability yields the following trend of decreasing stability: 4,5-methanoprolyl > prolyl > 3,4-methanoprolyl. Additionally, beta-branching on the amino acid moiety confers added stability, with beta-quaternary center-containing compounds best overall. Interestingly, though one might predict that substitution on the amine-N as in the

Novartis compound BMS-428245 (DPP-728) would provide a steric impediment to cyclization onto the nitrile (the most likely mechanism contributing to solution instability at neutral pH based on the literature), this compound behaves similarly to other non-cyclopropanated compounds. These preliminary data support additional benefit to the presence of the 4,5-methanoprolyl residue beyond the critical role played in securing proprietary coverage.

Table 1. Solution stability of selected DP4 inhibitor compounds

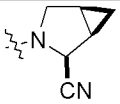
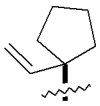
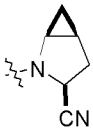
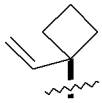
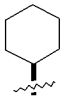
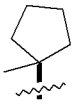
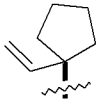
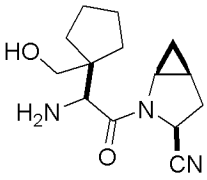
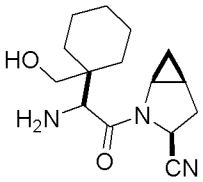
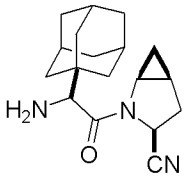
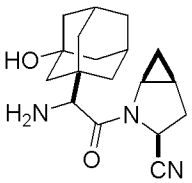
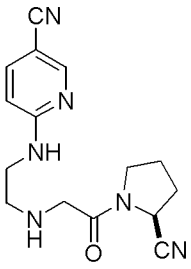
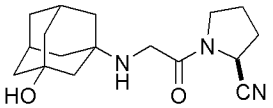
BMS #	proline moiety	amino acid moiety	% remaining after 4 h		% remaining after 24 h	
			pH 1.1	pH 7.2	pH 1.1	pH 7.2
440617			97.93	25.43	94.36	0
430516	"		98.62	48.28	96.34	4.94
420597			100	54.42	99.72	7.21
439421	"		100	66.53	99.75	20.27
428245	"	**Novartis DPP-728**	100	75.97	98.33	24.43
440823			99.85	77.59	99.63	27.16
395067	"		100	84.80	100	37.50
442371	"		100	81.88	100	46.28
356379	"		100	86.95	100	47.66
405295	"		99.94	94.01	100	74.19
431285	"		99.4	88.1	nd	
431289	"		97.6	92.9	nd	nd
429636	"		100	95.10	98.69	73.33
430452	"		100	95.94	100	79.01

Table 2. In vitro, in vivo, and PK data for selected DP4 inhibitor compounds.

compound	isolated porcine DP4 K_{is} (nM)	rat *ex vivo* plasma DP4 inhibitory ED_{50} (μmol/kg, p.o.)	PK (rat)	CYP450 inhibition (μM)
 **BMS-465980**	6.7 slow-binding	30 min 0.4 2 hour 3.3 4 hour 5 6 hour 11	%F 59 $t_{1/2}$ 1.25*	1A2 >100 2C9 >100 2C19 99 2D6 >100 $3A4_{BFC}$ 96 $3A4_{BzRES}$ 77
 **BMS-477121**	29.0 slow-binding	TBD	TBD	1A2 TBD 2C9 TBD 2C19 TBD 2D6 TBD $3A4_{BFC}$ TBD $3A4_{BzRES}$ TBD
 **BMS-469767**	14.7 slow-binding	30 min 0.1 2 hour nd 4 hour 0.4 6 hour nd	%F 2.2 $t_{1/2}$ 1.35	1A2 >100 2C9 >100 2C19 >100 2D6 >100 $3A4_{BFC}$ 23 $3A4_{BzRES}$ 22
 **BMS-477118**	18.9 slow-binding	30 min 0.12 2 hour 0.2 4 hour 0.3 6 hour 0.5	%F TBD $t_{1/2}$ TBD	1A2 >100 2C9 activ'n 2C19 >100 2D6 >100 $3A4_{BFC}$ >100 $3A4_{BzRES}$ activ'n
 **BMS-428245 (Novartis)**	7.6	30 min 3.2 2 hour nd 4 hour >100 6 hour >100	%F 96 $t_{1/2}$ 2.3	1A2 >100 2C9 >100 2C19 >100 2D6 >100 $3A4_{BFC}$ >100 $3A4_{BzRES}$ activ'n
 **BMS-471211 (Novartis)**	50.6 slow-binding	30 min TBD 2 hour TBD 4 hour TBD 6 hour TBD	%F 96 $t_{1/2}$ 1.73	1A2 >100 2C9 >100 2C19 >100 2D6 >100 $3A4_{BFC}$ >100 $3A4_{BzRES}$ >100

* approximation only, evidence of enterohepatic recirculation

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