

Timetable of the development of Fesoterodine

Date	Event / Topics	Participants/ Author	Major Points and Decisions	Attachment/Reference
CW 34, 1997	Discussion of research proposal on prodrug of tolterodine metabolite (DD 01) made by BS (letter)	LE, PN	PN to initiate project evaluation	
28.08.1997	Project discussion, identification of potential prodrug candidates	BS, COM, PN	Derivatization of the benzylic hydroxy group of DD 01 appears most promising; concentrate initially on synthesis of tolterodine metabolite. COM to prepare first chemical development plan;	(1) handwritten notes of COM
19.09.1997	First Team Meeting: - Project Definition - Patent issues - Chemical development plan - Preclinical development plan	LE, UK, COM, PN, DS, BS	Proposed structures are not patent protected; synthetic work started Sept. 15; work on chemical plan with highest priority	(2) Meeting minutes incl. attachments
03.10.1997	1 st Update of Chemical Development Plan	COM		(3) 1 st update of ChDP
24.10.1997	Second Team Meeting	HB, LE, COM, PN, DS, BS	First choice are acetyl or benzyl derivatives; draft study protocol "BA dog" finalized; start second draft of "mock patent"	(4) Meeting minutes incl. attachments (e.g. 2 nd update of ChDP)
02.12.1997	Third Team Meeting	HB, LE, UK, COM, PN, DS, BS	First prodrug (racemic acetate of benzyl ether available) Bioanalytical methods for tolterodine and DD 01 available; BA study scheduled to start as soon as substances are available; first draft of "mock patent" available	(5) Meeting minutes incl. attachments (e.g. 3 rd update of ChDP)
02.01.1998	Status Report Chemistry	COM	Problems in derivatization at the benzylic hydroxy group and potential solutions	(6) Confidential Status Report Incontinence Project

10.02.1998	4 th Update of Chemical Development Plan	COM	Pure hydroxy metabolite (DD 01) available, scale-up ongoing; 5 benzylic monoacyl esters available, but chemically unstable; S9 assay established, testing of prodrugs for metabolization ongoing	(7) 4 th update of ChDP
20.02.1998 23.03.1998	5 th Update of Chemical Development Plan	COM	Scale-up of pure hydroxy metabolite (DD 01) ongoing; 22 potential prodrugs so far synthesized and tested in S9 assay; best formation of HO/OH by AcO/OAc, iButO/iBut and HO/OiBut	(8) 5 th update of ChDP and attachments (handwritten notes ; Report on S9 experiments)
25.06.1998	Team Meeting "NCE Incontinence"	HB, CM, PN, BS	Patent application filed May 12, 1998; work on synthesis of pure enantiomers ongoing; 1 st BA study in dogs with SPM 8163, 6650, 7528, 8168, 7527 and 6656 started May 5, 1998; data on Caco cell experiments available	(9) Meeting minutes incl. attachments (e.g. 6 th update of ChDP)
10.08.1998	Team Meeting "NCE Incontinence"	CA, HB, COM, PN, DS, BS	First positive results on availability of enantiomers; BA study in dogs finalized, first analytical results available; decision to move forward with HO/OCOR compounds; first data on skin penetration available	(10) Meeting minutes incl. attachments (e.g. 7 th update of ChDP)

BA Bioavailability ChDP Chemical Development Plan

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Dates of availability of racemic prodrugs

SPM	Kürzel	Datum Laborprotokoll
7500	HO/OH	8.1.98
8163	HO/OHxHCl	9.3.98
6651	EtO/OHxmes	9.3.98
6645	MeO/OH	15.1.98
6656	EtO/OHxHCl	24.3.98
8146	PivO/OPIV	10.3.98
8150	iButO/OH	20.1.98
8151	PivO/OH	22.1.98
8148	BzO/OH	19.1.98
7513	HO/OAc	11.3.98
7511	HO/OnProp	10.3.98
7512	HO/OnBut	10.3.98
7504	HO/OiBut	16.2.98
7527	HO/OiButxHCl	29.4.98 (?)
7496	HO/OPIV	4.3.98
7468	HO/OBn	27.11.97
7501	AcO/OAc	15.1.98
7514	nPropO/OnProp	11.3.98
7503	PivO/OPIV	23.2.98
8132	AcO/OBn	26.11.97
7471	BzO/OBn	4.12.97

SPM number	Abbreviated substitution pattern (benzyl side / phenyl side)	Date of availability (according to lab data records)
8132	AcO / OBn	26.11.1997
7468	HO / OBn	27.11.1997
7471	BzO / OBn	04.12.1997
7500 (DD 01)	HO / OH	08.01.1998
7501	AcO / OAc	15.01.1998
6654	MeO / OH	15.01.1998
8148	BzO / OH	19.01.1998
8150	iButO / OH	20.01.1998
8151	PivO / OH	22.01.1998
7504	HO / OiBut	16.02.1998
7503	PivO / OPIV	23.02.1998
7496	HO / OPIV	04.03.1998
6651	EtO / OH x mesylate	09.03.1998
8163	HO / OH x HCl	09.03.1998
8146	nButO / OH	10.03.1998
7511	HO / OnProp	10.03.1998
7512	HO / OnBut	10.03.1998
7513	HO / OAc	11.03.1998
7514	nPropO / OnProp	11.03.1998
6656	EtO / OH x HCl	24.03.1998
7527	HO / OiBut x HCl	29.04.1998

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