Technical Development Plan

Project: SDZ ENA 713 TDS
Indication: Demetia of the Alzheimer's Type
Galenical Form: Transdermal Patch
Dosage strengths: **Service Form:** Not yet determined. [10 cm^2 (6mg), 20 cm^2(12 mg), 30 cm^2(18 mg), 40 cm^2 (24 mg)]
Market Form: Not yet determined

I. General

TechR&D-ITM: K.A. Bergmann
Subteam-members: H. Boehnke, O. Garinot, J-P. Nougaret, H. Tiemessen

Phase: DC
Next decision points: Interim Decision Point, Jan 1996

First appl. for clin. trial authorization: First trial performed in 1991
IND target date: January 1996
RDP target date: August 2000

Next update: December 1995

II. Product Rationale

1. Technical Product Profile: The ENA 713 TDS is a simple, elegant, single layer matrix system with drug and adhesive combined and then applied to a backing. The patient's skin acts as the rate controlling barrier. The final clinical service form currently being developed will deliver 12 mg/ 20 cm^2/ 24 h. Other dosage strengths will be provided by varying the size of the patch. The system will be loaded with approximately 34 mg of ENA 713 base, thus delivering about 30% of its contents over 24 h.

2. Development Strategy: The rationale for development of a transdermal delivery system of ENA 713 is manifold. Improved safety and tolerability provide the foundation for other benefits from this dosage form. Single transdermal doses of 12 mg/ 24 h were tolerated in healthy male subjects with no adverse events different from those observed with placebo. The highest single oral dose tolerated in healthy males was 3 mg. In clinical trials in patients, after a 9-10 week titration phase, nausea and vomiting were the most frequent dose limiting adverse events. These adverse events have not yet been observed with the TDS, in single dose studies.

   The ENA 713 TDS would allow once daily dosing, as opposed to bid or tid dosing used with the oral form. The TDS would allow us to be competitive with other once daily oral forms and other transdermal forms. There is the possibility that greater efficacy could be achieved with the TDS as opposed to oral ENA 713 because higher doses would be tolerated or greater numbers of patients would be able to tolerate doses currently used in the core program.

   Because the oral form of ENA 713 was developed first and is further along in development, it is planned to proceed to Phase II/III trials with the oral form and in parallel, to pursue the TDS, which, if found to be efficacious could enter the market 3 years after the oral form. The most critical issue is whether the efficacy of ENA 713 is tied to sharp peaks and troughs, as seen with the oral form, or whether a smoother profile, with lower peaks and greater AUC's will work just as well. Only large Phase II/III trials will be able to answer such a question.

Drug Substance:

Key activity	Important issues	Depart-ment	Deadline
Salt selection program	Base selected, as needed to increase flux rate	DDS	Done
Process development, manufacture and release of technical batch	1 kg batch will be provided by CFE by August 94	CFE AFE	Aug 94
Establishment of analytical methods	first experience with drug substance as liquid	TRD-F	Oct 94
Investigation of substance properties		TRD-F	Oct 94
Radioactive labelling	Not Determined	--	--
Manufacture and release of Phase I batch	5 kg batch planned	CFE TRD-F	Jan 95
Manufacture and release of technical batch	26 kg batch planned	CFE TRD-F	June 95
Selection of production site	PBO planned	CFE	
Manufacture and release of Phase II batch (prototype adequate)	15 kg batch planned	CFE TRD-F	Dec 95
Manufacture and release of technical batch	52 kg batch planned	CFE TRD-F	July 96
Manufacture and release of prototype batch	78 kg batch planned	CFE TRD-F	April 97
Prototype declaration / Technological Acceptance		CFE TRD-F	April 97
Registration Activities		DOC	Nov 97

Service Form:

Key activity	Important issues	Depart-ment	Deadline
Preclinical stability studies	with research batch of 50 gm	AFE	June 94
Development, manufacture and release of Provisional Service Form		LTS	June 95
Development, manufacture and release of Parenteral Service Form	Done	--	--
Development, manufacture and release of Definitive Service Form	**Time critical depending on changes needed	LTS	July 96
Evaluation of (unusual) excipients	Durotak is being investigated	TRD-DOC	Dec 94
Manufacture and release of positive controls	Not Needed	--	--
Development of primary packaging	Tight packaging required	LTS	July 96
Registration Activities	IND filing expected January 96	DOC	Dec 95

Market Form:

Key activity	Important issues	Depart-ment	Deadline
Preformulation studies		LTS	July 96
Laboratory batch phase		LTS	June 95
Evaluation of (unusual) excipients	Duratak is being investigated	TRD-DOC	Dec 94
Development of primary packaging		LTS	July 96
Selection of production site	LTS has worldwide manufacturing rights, sites in Germany and USA	DDS	Done
Pilot batch phase		LTS	July 96
Development of secondary packaging		PMD	Mar 98
Handover batch phase	Not Needed		
Production scale-up batches	First production scale-up batch, to be used for clinical supplies for Phase III, due Nov 97	LTS	Oct 98
Technological Acceptance / Prototype declaration		DDS	Jan 99
Manufacture and release of positive controls	Not Needed		
Registration Activities	RDP expected for August 2000		

IV. Costs, Capacities

Project classification (L, M, H):

Phase	Date of transfer	Capacities (FTE's)				Total Costs (Mio SFr.)
		CHRD	ARD	GRD	Others (1)	external
IC						
DC	June 94	6.0	2.0	1.1	0.4	0.98
Phase I	Nov 95	3.8	2.7	1.1	0.9	0.45
Phase II	Sept 96	0.8	4.1	2.0	0.9	1.64
Phase III	March 98	-	14.5	4.5	3.0	-

(1) e.g. TechR&D-DOC, logistics

V. Technical hurdles

Hurdle	Probability	Impact (2)
Stability / Quality of Base	15 %	6 mo delay
Stability of Patch	20 %	9 mo delay + cost
Flux insufficient in vivo	30 %	9 mo delay + cost

(2) Impact: D= delay (months), C= cost increase (please specifiy), T= termination

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