NCE-Incontince Meeting
Monheim, May 28, 1999

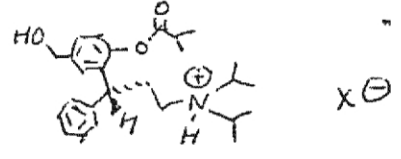**Participants:**

C. Arth

H. Boekens

C. van Dorp

H. Friehe

C. Meese

P. Ney

A. Schuetz

B. Sparf

Preclinical Development
− 7 JUN 1999
signature: _____

SYNTHESELABOR
0 4. Juni 1999

The selected candidate is: H0/0iBut

This means : →

In SPM 8228 "x⊖" is chloride. This salt, however, is amorphous and hygroscopic. We shall look now for ~ 20 other salts to improve the physicochemical properties. Claus

> **PRIVILEGED**

2. Chemistry (C. Meese)

C. Meese explained the present route of synthesis (attachment 1). The aim is to get about 60 - 70 g of H0/0iBut in the lab-scale and about 0,5 kg of H0/0iBut in the kilo-lab-scale by the mid of July. A stable and crystalline salt is requested: Reference standards for H0/0H and H0/0i But with certificates of analysis are requested.

3. Biological (H. Boekens)

The PK-results of the second bioavailable study in dogs are complete. They demonstrate that the half-life of tolterodine is shorter and the bioavailability of the metabolite is less than after application of H0/0iBut (attachment 2). Method development for tox study has been started and method validation for rats and dogs is ongoing.

4. Development Plan (P. Ney)

In order to put a development plan together, timelines and concepts for all necessary chemical, pharmaceutical and preclinical activities have been discussed. Cost estimations of the departments have to be given to P. Ney. H0/0iBut is called SPM 8228 for the moment. This number will be changed due to the internal system as soon as a salt is known.

5. Milestone decision

0H/0iBut has been selected as drug candidate for the NCE-incontinence project.
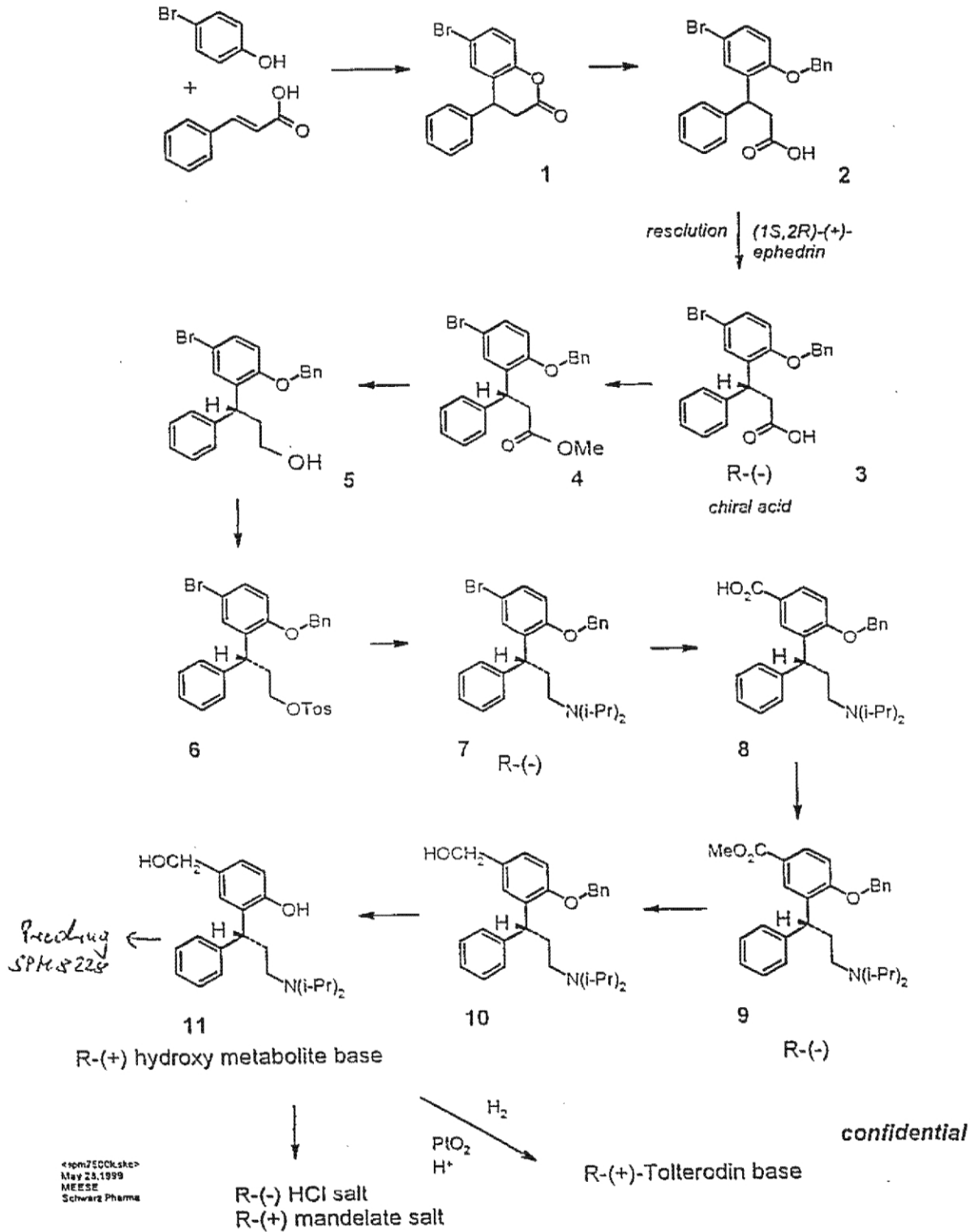
6. Actions until board presentation

- Development Plan (P. Ney)
- Cost estimations of the departments have to be given to P. Ney asap.

A. Schütz
May 31, 1999

SP Modification of the P & U Route

Present Process, May 28, 1999

Br—⬡—OH

+

(cinnamic acid) OH / O

→ **1**

→ **2**

resolution | (1S,2R)-(+)-ephedrin

5 / **4** / R-(-) **3**

chiral acid

6 (OTos) / **7** R-(-) / **8**

11 / **10** / **9** R-(-)

R-(+) hydroxy metabolite base

Prodrug ← SPM 8228

R-(-) HCI salt
R-(+) mandelate salt

H₂
PtO₂
H⁺
→ R-(+)-Tolterodin base

confidential

<spm7500k.ske>
May 23.1999
MEESE
Schwarz Pharma

1 Study Summary

Sponsor:	SCHWARZ PHARMA AG, Monheim (Germany)
Study Responsible:	Dr. P. Ney, Dept. NPTA

Testing Facilities
Administration and plasma sampling:

	LPT, Hamburg (Germany)	
	Study Director:	Dr. phil. J. Leuschner
	Protocol No.:	LPT 11997/1/99
Bioanalytics:	SCHWARZ PHARMA AG, Monheim (Germany)	
	Study Director:	Dr. W. Hammes, Dept. BA
	Analytical Report:	BA 304-02

Test Substances:	SPM 5427, SPM 6723, SPM 6725, SPM 8228, SPM 8229, SPM 8230 and SPM 9078
Dose Level:	0.3 µmol/kg b.w.
Animals:	5 Beagle dogs (male / age: *to be amended* / b.w. 10 - 15 kg)
Design:	8-way cross-over design. Single doses of the test substances were administered according to the following scheme. All administrations were separated by a wash-out phase of at least two days.

Substance	Batch No.	Route	Dose Level [µmol/kg b.w.]	test day	dogs
SPM 5427 [(+)-HO-/-OH*HCl]	AB-5430	i.v.	0.3	1	1 - 5
	f	p.o.	0.3	5	1 - 5
SPM 6723 [(+)-BzO-/-OBz*HCl]	RK-6723	p.o.	0.3	9	1 - 5
SPM 6725 [(–)-AcO-/-OBz*HCl]	RK-6725	p.o.	0.3	12	1 - 5
SPM 8228 [(+)-HO-/-OiBut*HCl]	AC-8228	p.o.	0.3	15	1 - 5
SPM 8229 [(+)-AcO-/-OiBut*HCl]	AC-8229	p.o.	0.3	20	1 - 5
SPM 8230 [(+)-HO-/-OBz*HCl]	AC-8230	p.o.	0.3	23	1 - 5
SPM 9078 [(+)-(R)-H-/-OH*Tart.]	FP-9092	p.o.	0.3	26	1 - 5

Samples:	EDTA plasma samples containing sodium fluoride
	i.v.: -10 (predose), 5, 10, 20, 40, 60 min and 2, 3, 4, 6 and 8 h
	p.o.: -10 (predose), 20, 40, 60 min and 2, 3, 4, 6 and 8 h
Bioanalytics:	determination of SPM 5427 plasma levels and of SPM 9075 plasma levels (test day 26 only) by GC-EI-MS/MS, bql: 0.040 ng/ml
Study Dates:	date of final protocol March 1st, 1999
	start of administration: March 18th, 1999

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