Division of Anesthesia, Analgesia and Rheumatology Products

Summary of Clinical Review of Studies submitted in Response to the Pediatric Written Request for NDA 20-998, Supplement 021

Application: NDA 20-998/SE5-021

Applicant: G.D. Searle L. L. C.
c/o Pfizer Inc.
235 E. 42nd Street
New York, NY 10017

Product: Celebrex® (celecoxib)

Pharmacologic Class: Non-selective Non-Steroidal Anti-inflammatory Drug (NSAID)/COX-2 Selective Inhibitor

Route: Oral

Formulations: 50-mg and 100-mg capsules

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I. BACKGROUND

Pfizer, Inc. submitted this efficacy supplement to their NDA 20-988 in support of marketing approval for Celebrex® (celecoxib) 50-mg and 100-mg capsules on June 20, 2006, for the treatment of the signs and symptoms of Juvenile Rheumatoid Arthritis (JRA) in patients 2 years of age and older.

Celeberex® was approved for adult patients with osteoarthritis (OA) and rheumatoid arthritis (RA) on December 31, 1998. The Division of Analgesia, Anti-Inflammatory and Ophthalmic Drug Products issued a pediatric Written Request (PWR) on January 25, 2002 pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act, to Pharmacia Corporation (acquired by Pfizer, Inc., April 2003). Pfizer responded to the PWR on June 20, 2006 with the submission of NDA 20-998, Supplement 021, consisting of one Phase 3 efficacy and safety study, and four pharmacokinetic studies. The Food and Drug Administration (FDA) granted Pfizer six months of additional marketing exclusivity for celecoxib on August 23, 2006 based on the study of an oral suspension of celecoxib in patients with JRA.

One of the results of the withdrawal of Vioxx from the market in September of 2004 due to safety concerns is that an increased level of scrutiny has been be applied to COX-2 Inhibitor, and to all NSAID drug products, by the Agency, the pharmaceutical industry, academia, the press, various advocacy groups and Congress. As part of this process, numerous analyses of the available data regarding the potential cardiovascular toxicity of Celebrex® have been performed, and numerous articles have been published on this subject. To date, while there is a fairly clear signal of increased risk for cardiothrombotic adverse events in adults, the exact degree of this risk and the underlying pathophysiology for these events remain controversial. In light of these findings in adults, and because of the particularly vulnerable nature of the patients that comprise the JRA population, this application was brought to the Arthritis Advisory Committee for discussion and recommendations on November 29, 2006. A complete transcript of that meeting will be available on the FDA web page in the near future.

II. REGULATORY ACTION

After careful consideration of the deliberations of the Advisory Committee at the meeting, the decision to approve this application was based on the serious nature of JRA, the lack of adequate available therapies, and the data submitted by the applicant which supports the position that the efficacy and safety profile for celecoxib for the duration of the study is comparable to what was observed with the active comparator. However, it is also understood that the major safety concern is about the potential for adverse events that will most likely manifest themselves years after treatment with celecoxib has been initiated. Nevertheless, we concur with the Advisory Committee members that the risk:benefit ratio is such that celecoxib would be an useful addition to the treatment armamentarium. We also concur that with the Committee members that additional safety information on the extended periods of treatment will need to be collected, via the completion of post-marketing commitments by the applicant.

III. POST MARKETING ACTIONS

During the course of their discussions, the Advisory Committee voiced their opinion that new therapies are needed for the treatment of JRA, not only because of the variability of responses to NSAIDs that is seen among patients, but because by increasing the alternatives available in the treatment armamentarium, the use of more toxic therapies can be potentially postponed. Further, they noted that celecoxib's twice daily dosing schedule has a higher probability of achieving patient compliance, and that even though a suspension is desirable, the fact that celecoxib can be administered as a sprinkle over applesauce is a helpful property of the formulation.

Discussion of celecoxib's safety profile revolved around its potential for thromboembolic adverse events and the need to further evaluate its implications for the JRA patient population. Suggestions included further studies to assess the safety profile beyond the 12-week period studied during the double-blind portion of the study, appropriate language in the label, and the creation of a patient registry that would follow patients for an extended period of time.

Risk Management Activity

There are no specific risk management activities necessary for this application.

Required Phase 4 Commitments

There are no required Phase 4 commitments.

Other Phase 4 Requests

As part of the follow-up to the recommendations made by the Advisory Committee, conversations were held with the applicant to discuss the type of post-marketing commitments and agreements that they would be able to perform.

The applicant proposed the following post-marketing commitment:

1. To conduct a short-term study to assess the additional risks due to celecoxib exposure, including blood pressure increases and gastrointestinal toxicity. The study would be a 6-week, randomized, open-label study in approximately 200 patients randomized in a 1:1 ratio to either celecoxib or naproxen.

The applicant also proposed the following agreements:

1. Standard Pharmacovigilance Plan
   Review of all adverse event reports collected from post-marketing surveillance, population based registries and ongoing clinical studies.
2. Enhanced Pharmacovigilance Activities
   a. Active Surveillance
      Routine survey will be conducted of pediatric networks, such as the Childhood Arthritis and Rheumatology Research Alliance, and pediatric specialties (pediatric rheumatologists, pediatric orthopedists, pediatric surgeons, and pediatricians).
   b. Prospective Observational Registry

Creation of a multicenter prospective observational registry to collect long-term safety, efficacy, and developmental data on patients treated with celecoxib or nonselective NSAIDs. The registry would enroll approximately 400 patients, 50% of whom will be followed for 2 years and 15% of whom will be followed for at least 3 years.

c. Creation of an Independent Pediatric Expert Panel
A panel will be created to review the safety data generated from the prospective observational registry, as well as from the post-marketing surveillance. The intent of the panel would be to monitor for evidence of cardiovascular thromboembolic events and gastrointestinal tolerability.

IV. SUMMARY OF CLINICAL FINDINGS

Data from Study N49-01-02-195 (referred to in this summary as "Study 195") was submitted in support of this application was a 3-month, randomized, double-blind, active controlled study comparing celecoxib 12 mg/kg/day and celecoxib 6 mg/kg/day with naproxen 15 mg/kg/day. The primary endpoint was the percent of patients achieving a JRA DOI (definition of improvement) 30. The study was designed to rule out a margin of non-inferiority of celecoxib to naproxen exceeding 25% based on the 95% confidence interval. As described above, the trial was successful in establishing non-inferiority of both doses of celecoxib to naproxen based on the prespecified 25% margin. Furthermore, improvements were seen in all the components of the JRA DOI-30: physician and parent global assessment, functional ability, joints with limited range of motion and C-reactive protein.

Data are available on the safety of treatment of JRA patients with celecoxib for up to 6 months at or above a dose approximating the dose proposed for marketing. In Study 195, 242 children were randomized to receive celecoxib 6 or 12 mg/kg/day or naproxen 15 mg/kg/day for 3 months. Following completion of the randomized, double-blind portion of the study 202 children enrolled in the open-label extension portion during which they received celecoxib 12 mg/kg/day for an additional 3 months. In the randomized portion of the trial for the celecoxib dose arm that approximates the dose proposed for marketing (6 mg/kg/day) the organ systems with the most common adverse events (AEs) were GI, infections and infestations and nervous system disorders. Compared to naproxen the only organ systems with more frequent AEs in the celecoxib 6 mg/kg/day arm were respiratory disorders, eye disorders and metabolic disorders. Overall, the common AEs seen with celecoxib 6 mg/kg/day were similar in type and frequency to those seen with naproxen.

Serious adverse events (SAEs) were observed more frequently in the celecoxib 6 mg/kg/day arm than with naproxen but there was no dose response as SAE rates were similar with celecoxib 12 mg/kg/d as with naproxen. The SAEs that were seen more frequently with celecoxib included GI disorders, General Disorders and Administration Site Conditions and Musculoskeletal, Connective Tissue and Bone Disorders. Skin reactions and allergic reactions were also observed. Overall the serious adverse events and severe adverse events observed with celecoxib represented events seen in this patient population and events known to be associated with other NSAIDs.

Brief Overview of Clinical Program

Celebrex (celecoxib) is a selective cyclogenase-2 (COX-2) inhibitor which inhibits prostaglandin synthesis and is indicated in adults for the relief of the signs and symptoms of osteoarthritis (OA) and adult rheumatoid arthritis (RA), acute pain and primary dysmenorrhea, ankylosing spondylitis (AS). In NDA 20-998 pediatric Supplement 021, celecoxib was studied for the indication of relief of signs and symptoms of juvenile rheumatoid arthritis (JRA) in patients ≥ 2 years to ≤ 17 years old.

Data submitted in support of this application were generated from the following studies:

1. Study N49-01-02-195
   Clinical trial in patients with JRA, as support for the safety and efficacy of celecoxib.
2. Study N49-98-02-088
   Clinical pharmacology study in healthy adults assessing the food effect on the PK of celecoxib capsules.
3. Study A3191162
   Clinical pharmacology study in healthy adults assessing the relative bioavailability of the celecoxib suspension compared to celecoxib capsules.
4. Study A3191202
   Clinical pharmacology study in healthy adults assessing the bioavailability of celecoxib when the capsule contents are sprinkled onto applesauce, compared to the intact capsule.
5. Study RR-754-00049
   A sub-study within Study N49-01-02-195 which assessed the PK of the celecoxib suspension in patients with JRA, utilizing population pharmacokinetic analyses, as compared to adult patients with rheumatoid arthritis who were administered the celecoxib suspension for 14 days.

Efficacy

Data from one clinical trial has been submitted as evidence of safety and efficacy in the new patient population. Study 195 was a randomized multicenter study which compared two doses of a celecoxib suspension to an active comparator. It had a 12-week double-blind period followed by an optional open-label treatment period for an additional 12 weeks.

STUDY DESIGN

Study 195 was a multicenter, randomized, double-blind, active comparator-controlled, parallel-group study which evaluated the safety and efficacy of a high-dose and a low-dose of a celecoxib suspension during a 12-week period, compared to a Naproxen suspension. Patients were randomized to one of the following three arms:

- Celecoxib suspension (50 mg/5 ml), approximately 3 mg/kg BID (6 mg/kg/day)
- Celecoxib suspension (100 mg/5 ml), approximately 6 mg/kg BID (12 mg/kg/day)
- Naproxen suspension (125 mg/5 ml), approximately 7.5 mg/kg BID (15 mg/kg/day)

Rather than administering to the patients the specific volume of the suspension that would result in the specified mg/kg dose, the applicant opted to utilize a dosing schedule where a discrete volume of the suspension was administered to patients, based on their weight and where it fell in

pre-specified categories. This is summarized in the following table, which identifies how the study drugs were to be administered in Study 195.

Table 1: Dosing Scheme for Administration of Study Drugs

Patient Weight	Bottle A	Bottle B
9 – 12 kg	2.5 ml	2.5 ml
13 – 25 kg	5 ml	5 ml
26 – 37 kg	7.5 ml	7.5 ml
38 – 50 kg	10 ml	10 ml
> 50 kg	15 ml	20 ml

The implications of this type of dosing scheme are that patients at the two ends of the weight band will be either overdosed (at the lighter end of the weight category) or under dosed (at the heavier end of the weight category). However, from a logistical perspective of dosing administration, it is clear that a dosing scheme that utlizes intervals of 2.5 ml will make it easier to administer the individual doses. Furthermore, although there were outliers at either extreme, the majority of the patients received very close to their assigned dose.

After the 12-week period, patients were eligible to enter an open-label extension phase for an additional 12 weeks. These patients would receive approximately 6 mg/kg BID (12 mg/kg/day) regardless of which arm they had been randomized to during the double-blind phase. The purpose of this phase was to assess the tolerability and effectiveness of chronic administration of celecoxib.

The primary efficacy endpoint was the proportion of patients who had a 30% or greater improvement in the Juvenile Rheumatoid Arthritis Definition of Improvement criteria, also known as the "JRA DOI-30." The JRA DOI-30 consists of six core variables, and in order to meet the responder definition a patient must have ≥ 30% improvement in 3 of these variables, *and* if there is >30% worsening, it can not be in more than one variable. The six variables are:

- Physician Global Assessment of Disease Activity
- Patient/Parent Assessment of Overall Well-being
- Functional ability (measured by Child Health Assessment questionnaire)
- Number of joints with active arthritis
- Number of joints with limited range of motion
- Laboratory markers of inflammation (C-reactive protein)

Secondary endpoints included the Parent's Assessment of the Child's Arthritis Pain, the Pediatric Quality of Life Inventory, additional definitions of improvement utilizing the JRA DOI (JRA DOI-50, JRA DOI-70), and evaluation of the JRA DOI-30 separately in patients with pauciarticular compared to patients with polyarticular JRA.

RESULTS

The study involved 60 clinical sites in Canada, Europe, South America, and the United States. Two hundred forty-two patients with JRA were randomized, and each had at least one dose of study drug, therefore, the safety population also consisted of 242 patients. During the double-

blind phase of the study, 77 patients were randomized to the low-dose celecoxib treatment arm, 82 patients were randomized to the high-dose celecoxib arm and 83 patients were randomized to the naproxen treatment arm.

The baseline demographics were generally balanced at baseline across the three treatment groups with respect to age, gender, race, height and weight. They were also balanced with respect to the duration of JRA, and the type of JRA onset (pauciarticular, polyarticular, and systemic).

The disposition of the patients during the 12-week double-blind period is summarized below.

Table 2: Patient Disposition during 12-Week Double Blind Phase of Study 195

	Celecoxib ~ 6 mg/kg/day N (%)	**Celecoxib ~ 12 mg/kg/day N (%)**	**Naproxen ~ 15 mg/kg/day N (%)**	**Total N (n%)**
Randomized to double-blind phase	77 (100)	82 (100)	83 (100)	242 (100)
Completed double-blind phase	67 (87)	71 (87)	74 (89)	212 (88)
Early withdrawal from double-blind phase	10 (13)	11 (15)	9 (11)	30 (12)
Reason for Withdrawal				
Adverse event	3 (4)	7 (9)	3 (4)	13 (5)
Protocol violation	0	1 (1)	1 (1)	2 (1)
Consent withdrawn	4 (5)	2 (2)	1 (1)	7 (3)
Lost to follow up	1 (1)	0	0	1 (1)
Lack of efficacy	2 (3)	1 (1)	4 (5)	7 (3)

Of the 212 patients eligible to enroll in the open-label phase, 202 enrolled and 195 completed the additional 12 weeks. The reasons for not enrolling in the open-label phase included protocol violations, withdrawal of consent, lack of efficacy, and decision by sponsor. The reasons for not completing the open-label phase were adverse event, protocol violation, withdrawal of consent, and protocol specific withdrawal criteria. These are summarized in the table below.

Table 3: Patient Disposition during the Open-Label Phase of Study 195

	Celecoxib ~ 6 mg/kg/day N (n%)	**Celecoxib ~ 12 mg/kg/day N (%)**	**Naproxen ~ 15 mg/kg/day N (%)**	**Total N (n%)**
Completed double-blind phase	67 (100)	71 (100)	74 (100)	212 (100)
Did not enter open-label phase	5 (7)	1 (1)	4 (5)	10 (5)
Reason for not entering double-blind phase				
Protocol violation	1 (1)	0	0	1 (0.5)
Consent withdrawn	3 (4)	1 (1)	3 (4)	7 (3)
Lack of efficacy	0	0	1 (1)	1 (0.5)

	Celecoxib ~ 6 mg/kg/day N (n%)	Celecoxib ~ 12 mg/kg/day N (%)	Naproxen ~ 15 mg/kg/day N (%)	Total N (n%)
Sponsor's decision	1 (1)	0	0	1 (0.5)
Enrolled in open-label phase	62 (100)	70 (100)	70 (100)	202 (100)
Completed open-label phase	60 (97)	66 (94)	69 (99)	195 (97)
Early withdrawal from open-label phase	2 (13)	4 (15)	1 (11)	7 (12)
Reason for Withdrawal				
Adverse event	1 (2)	1 (1)	1 (1)	3 (1)
Protocol violation	1 (2)	0	0	1 (0.5)
Consent withdrawn	0	2 (3)	0	2 (1)
Protocol specific withdrawal criteria	0	1 (1)	0	1 (0.5)

The most commonly occurring protocol violations were the use of a prohibited concomitant medication, analgesic medication exceeding the protocol-specified 3-day limit, and non-compliance with study medication.

PRIMARY EFFICACY ANALYSES

The applicant intended to demonstrate non-inferiority to the comparator, which the protocol specified as occurring if the lower limit of the 95% confidence interval for the difference between the percent of responders (celecoxib – naproxen) was above -25%. Both, the low-dose and high-dose celecoxib, treatment groups met the non-inferiority criterion. The results of the study for the primary efficacy endpoint are summarized in the table below:

Table 4: Efficacy of Primary Endpoint of Study 195

	Celecoxib ~ 6 mg/kg/day N = 77	Celecoxib ~ 12 mg/kg/day N = 82	Naproxen ~ 15 mg/kg/day N = 83
Number (%) of responders	53 (68.83)	66 (80.49)	56 (67.47)
Treatment Comparisons		*Difference*	*95 % Confidence Interval*
Celecoxib 6 mg/kg/day – Naproxen 15 mg/kg/day		+1.36%	(-13.08%, 15.80%)
Celecoxib 12 mg/kg/day – Naproxen 15 mg/kg/day		+13.02%	(-0.22%, 26.25%)

SECONDARY EFFICACY ANALYSES

Evaluation of the secondary endpoints demonstrated that both, the low-dose and the high-dose celecoxib treatment arms were non-inferior to the naproxen treatment arm.

SUBGROUP ANALYSES OF EFFICACY

An analysis was performed to assess whether there was any difference in efficacy in patients who were receiving concomitant methotrexate therapy during the double-blind phase of the study. Since the study was not prospectively powered to detect a difference between these groups, the numbers in the individual categories were small. However, numerical differences were seen in the low-dose celecoxib treatment arms, depending on whether methotrexate was a concomitant medication (higher point estimate for the JRA DOI-30 for the methotrexate-concomitant treatment group). No difference was seen for the high-dose celecoxib treatment group. The naproxen-treated group trended differently, with the methotrexate concomitant-treated group having a lower point estimate than the non methotrexate treated group.

Analyses of the secondary endpoints did not identify any clinically significant differences in trends across the core variables, with or without concomitant methotrexate administration.

OPEN-LABEL PHASE OF STUDY 195

The treatment effect that was observed at Week 12 was maintained through Week 24 in the patients who enrolled in the open-label phase of Study 195. This was observed in the analysis of the primary endpoint, as well as in the analyses of the secondary endpoints.

Safety

The safety database included 242 patients that were randomized into the 12-week double-blind phase, and 202 patients who entered the open-label phase. The duration of exposure, identified by the phase of the study, is summarized in the two tables below.

Table 5: Duration of Exposure, Double-Blind Phase

	Celecoxib ~ 6 mg/kg/day N (%)	**Celecoxib ~ 12 mg/kg/day N (%)**	**Naproxen ~ 15 mg/kg/day N (%)**
Number treated	77 (100)	82 (100)	83 (100)
Duration in Days			
1 – 29	8 (10)	6 (7)	2 (2)
30 – 59	1 (1)	5 (6)	5 (6)
60 – 93	65 (84)	71 (87)	69 (83)
> 93	3 (4)	0	7 (8)
Patient-years of exposure	17	18	19

Table 6: Duration of Exposure, Open-label Phase

	Previous Treatment Group		
	Celecoxib ~ 6 mg/kg/day N (%)	**Celecoxib ~ 12 mg/kg/day N (%)**	**Naproxen ~ 15 mg/kg/day N (%)**
Number treated	62 (100)	70 (100)	70 (100)
Duration in Days			

	Previous Treatment Group		
	Celecoxib ~ 6 mg/kg/day N (%)	**Celecoxib ~ 12 mg/kg/day N (%)**	**Naproxen ~ 15 mg/kg/day N (%)**
1 – 29	1 (2)	2 (3)	1 (1)
30 – 59	0	2 (3)	1 (1)
60 – 84	30 (48)	29 (41)	25 (36)
85 – 114	31 (50)	37 (53)	42 (60)
> 114	0	0	1 (1)
Patient-years of exposure	14	16	16

DEATHS

There were no deaths reported in any of the clinical trials supporting this efficacy supplement.

DISCONTINUATIONS

The most common reason for discontinuation from the low-dose celecoxib and the naproxen treatment groups were gastrointestinal adverse events. The most common reason for discontinuation in the high-dose celecoxib treatment group was abnormal laboratory findings (abnormal liver function tests, and hematuria).

SERIOUS ADVERSE EVENTS

There were 9 serious adverse events (SAEs) in Study 195, 5 of which occurred during the double-blind phase of the study. Three of the events were in the low-dose celecoxib treatment group and two of the events were in the high-dose celecoxib treatment group. The events reported are summarized in the table below:

Table 7: Serious Adverse Events

Patient ID Number, Age, and Gender	**Event**	**Comment**
Double- blind Phase		
Low-dose celecoxib treatment group		
1045, 15 yrs, female	Severe epigastric pain	Recovered
1303, 11 yrs, male	Acute viral illness	Recovered
1351, 8 yrs, female	Acute CMV hepatitis	Recovered
High-dose celecoxib treatment group		
1176, 6 yrs, male	Severe exacerbation of asthma	Recovered
1326, 13 yrs, male	Worsening of JRA pain	Recovered
Open-label Phase		
1088, 14 yrs, female	Severe epigastric pain and vomiting after an overdose of erythromycin and celecoxib	Recovered; had elevated CPK believed to be secondary to exercise
1044, 15 yrs, male	Flare of systemic symptoms of JRA, inflammatory myopericarditis	Had previous history of myopericarditis.

Patient ID Number, Age, and Gender	Event	Comment
1161, 12 yrs, male	Primary pulmonary tuberculosis	Treated for tuberculosis
1225, 7 yrs, female	Severe lymphadenopathy, pyrexia, sore throat, mild torticollis	Hospitalized; celecoxib temporarily discontinued, then resumed 48 hours later.

OTHER ADVERSE EVENTS

The most commonly reported adverse events for all three treatment groups were related to the gastrointestinal system (including abdominal pain, nausea, vomiting, and diarrhea). The incidence was comparable across the three treatment groups.

The second most commonly reported adverse event was coded to the "infections and infestations" category and included nasopharyngitis, upper respiratory infections, influenzae, tonsillitis, and urinary tract infections. The incidence was also comparable across the three treatment groups.

The third most common system affected was the "nervous system" which included events such as headaches, disturbances in attention, dizziness (excluding vertigo), hypoaesthesia and aggravation of migraines. Naproxen had a numerically higher incidence compared to the two celecoxib treatment groups.

Overall, the adverse events reported were consistent with the adverse event profile of NSAIDs/COX-2 selective inhibitors.

Dosing Regimen and Administration

The celecoxib doses in the double-blind phase of Study 195 were low-dose celecoxib (approximately 6 mg/kg/day) administered as a 50 mg/5 mL suspension and high-dose celecoxib (approximately 12 mg/kg/day) administered as a 100 mg/5mL suspension. In the open-label extension phase of Study 195, all patients were entered into a high-dose celecoxib treatment group, regardless of their treatment group assignment in the double-blind phase. The sponsor's proposed dosing for patients with JRA is based on total body weight: celecoxib capsule (50 mg) 50 mg BID (100 mg/day) for patients ≥ 10 kg to ≤ 25 kg, and 100 mg BID (200 mg/day) for patients > 25 kg.

(b)(4)

(b)(4) using the capsule formulation in order to provide a timely therapeutic alternative for patients with JRA.

Drug-Drug Interactions

Drug-drug interaction studies are reflected in the current label and were reviewed with the original NDA 20-998 submission.

Special Populations

The non-selective NSAID/COX-2 selective inhibitor, celecoxib, has been studied in adult special populations of geriatrics, adults with hepatic insufficiency and adults with renal insufficiency. Celecoxib has also been studied for pharmacokinetic differences by race under the original NDA 20-998. Clinical studies demonstrate gastrointestinal and cardiovascular safety issues with long-term administration of celecoxib in adult patients with various conditions. Currently, Pfizer is conducting a 20,000-person international trial to further assess the safety risks of long-term administration with celecoxib.

V. CONCLUSIONS AND RECOMMENDATIONS

1. The applicant submitted all the data requested in the Pediatric Written Request.
2. The data support granting the indication for the relief of the signs and symptoms of Juvenile Rheumatoid Arthritis in patients 2 years of age and older.
3. The dosing and administration support the following:

Pediatric Patients 2 years and older	**Dose**
≥ 10 kg to ≤ 25 kg	50 mg capsule twice daily
> 25 kg	100 mg capsule twice daily

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/s/

Bob Rappaport

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